

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

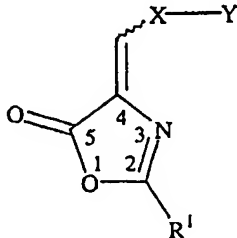
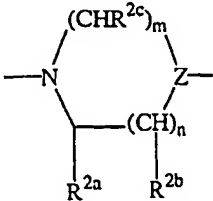
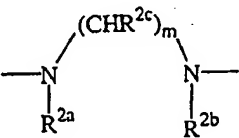
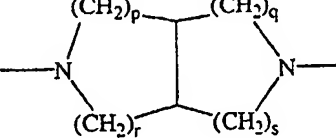
- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.**



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>7</sup> : <b>C07D 263/42, 413/00, 417/00, 487/04, A61K 31/421, 31/422, A61P 13/00</b></p>	<p><b>A1</b></p>	<p>(11) International Publication Number: <b>WO 00/55143</b> (43) International Publication Date: 21 September 2000 (21.09.00)</p>
<p>(21) International Application Number: PCT/EP00/02200 (22) International Filing Date: 13 March 2000 (13.03.00) (30) Priority Data: 60/124,781 17 March 1999 (17.03.99) US 60/124,721 17 March 1999 (17.03.99) US 60/165,312 12 November 1999 (12.11.99) US (71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; 124 Grenzacherstrasse, CH-4070 Basle (CH). (72) Inventors: COFFEN, David, Llewellyn; 5562 Caminito Exquisito, San Diego, CA 92130 (US). DILLON, Michael, Patrick; 1349 Rosewood Avenue, San Carlos, CA 94070 (US). FORD, Anthony, P., D., W.; 709 Tiana Lane, Mountain View, CA 94041 (US). GOGAS, Kathleen, Ruth; 2079 Pepperdine Drive, Los Banos, CA 93635 (US). JACOBSON, Lupita; 21295 Rumford Drive, Cupertino, CA 95014 (US). LI, Zhe; 3550 Lebon Drive, San Diego, CA 92122 (US). WILLIAMS, Timothy, James; 510 Castlerock Terrace, Sunnyvale, CA 94087 (US). (74) Agent: POPPE, Regina; 124 Grenzacherstrasse, CH-4070 Basle (CH).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: OXAZOLONE DERIVATIVES AND THEIR USE AS ALPHA-1 ADRENORECEPTOR MODULATORS</p> <div style="text-align: center;">  <p>(I)</p> </div> <div style="display: flex; justify-content: space-around; align-items: flex-end;"> <div style="text-align: center;">  <p>(A)</p> </div> <div style="text-align: center;">  <p>(B)</p> </div> <div style="text-align: center;">  <p>(C)</p> </div> </div> <p>(57) Abstract</p> <p>Compounds of Formula (I) wherein X is Formula (A), (B) or (C); Z is CH or N; R<sup>1</sup> is cycloalkyl, cycloalkenyl, heterocyclic, aryl or heteroaryl; are useful as alpha-1 adrenoreceptor modulators, particularly antagonists.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## OXAZOLONE DERIVATIVES AND THEIR USE AS ALPHA-1 ADRENORECEPTOR MODULATORS

Technical Field

5           The invention relates generally to oxazolone derivatives, and pharmaceutically acceptable salts or solvates thereof, which exhibit useful pharmacological properties. In particular, the invention relates to compounds, pharmaceutical compositions and methods of using oxazolone derivatives as alpha<sub>1</sub>-adrenergic receptor (alpha<sub>1</sub>-adrenoceptor) modulators, preferably  
10 antagonists.

Background of the Invention

Alpha<sub>1</sub>-adrenergic receptors are G-protein coupled transmembrane receptors that mediate various actions of the sympathetic nervous system  
15 through the binding of the catecholamines, epinephrine and norepinephrine. Currently, several subtypes of the alpha<sub>1</sub>-adrenergic receptors are known to exist for which the genes have been cloned: alpha<sub>1A</sub> (previously known as alpha<sub>1C</sub>), alpha<sub>1B</sub> and alpha<sub>1D</sub>. The existence of an additional subtype, the alpha<sub>1L</sub>-adrenergic receptor subtype, has been proposed; however, the gene for the  
20 alpha<sub>1L</sub>-adrenergic receptor subtype has yet to be cloned. Although these subtypes can be pharmacologically distinguished, existing subtype-selective compounds are only moderately specific and may interact with more than one alpha<sub>1</sub>-adrenergic receptor subtype. Accordingly, therapeutic use of nonselective alpha<sub>1</sub>-adrenergic receptor antagonists must be carefully monitored  
25 as such antagonists can produce significant undesirable side effects such as postural hypotension, sedation or depression, increased gastrointestinal motility and diarrhea, impaired ability to ejaculate, nasal stuffiness, akinesia and the like.

Non-selective alpha<sub>1</sub>-adrenoceptor antagonists have been used to treat lower urinary tract symptoms associated with benign prostatic hyperplasia (BPH).



Further, alpha<sub>1</sub>-adrenoceptor antagonists can be effective in reducing or alleviating urinary tract disorders and/or the symptoms thereof, such as pelvic hypersensitivity, overactive bladder, urinary frequency, nocturia, urinary urgency, detrusor hyperreflexia, outlet obstruction, prostatitis, incontinence, urge  
5 incontinence, urethritis, prostatodynia, idiopathic bladder hypersensitivity, and the like.

Compounds that interact more selectively with a particular alpha<sub>1</sub>-adrenergic receptor subtype may prove clinically useful in providing more selective treatment of conditions and diseases, and symptoms thereof,  
10 associated with activity at the receptor subtype. For example, alpha<sub>1</sub>-adrenergic receptor antagonists that can selectively reduce or alleviate urinary tract disorders or symptoms, or ameliorate nociceptive and/or neurogenic pain without affecting blood pressure or causing postural hypotension, are desirable. Presently available alpha<sub>1</sub>-adrenergic antagonists are either relatively  
15 nonselective with respect to the subtypes with which they interact or generally are not selective for the alpha<sub>1B</sub>-adrenergic receptor subtype.

#### Description of the Related Art

U.S. Patent No. 5,736,412 (Zambias *et al*) refers to a method of  
20 generating a plurality of certain chemical compounds in a spatially arranged array.

U.S. Patent No. 5,859,014 (Bantle *et al.*) refers to certain pyrimidinedione, pyrimidinetrione, triazinedione and tetrahydroquinazolinedione derivatives which are disclosed as being useful as alpha<sub>1</sub>-adrenergic receptor antagonists.

25 PCT Published Application WO 95/25726 (assigned to Recordati) refers to certain quinazolyl-amino derivatives which are disclosed as having alpha antagonist activity.

PCT Published Application WO 98/46551 (assigned to Arqule) refers to a synthesis and use of certain biased arrays.

30 PCT Published Application WO 98/46559 (assigned to Arqule) refers to a synthesis and use of certain alpha-ketoamide derivatives and arrays.

PCT Published Application WO 98/56028 (assigned to Arqule) refers to an automated, highthroughput method for screening a plurality of compounds using mass spectrometry.

PCT Published Application WO 96/16049 (assigned to Glaxo) refers to  
5 certain oxazoles as  $\alpha_1$ -antagonists.

PCT Published Applications WO 99/09979, WO 99/09980, and WO 99/09829 (all assigned to Eli Lilly) refer to certain oxazoles for treating neuropathic pain.

European Patent Application EP 602851 refers to certain quinazoline  
10 derivatives.

German Patent Publications No. 117 224, 117 225, 117 228 , and DE 2 659 543 refer to synthesis of certain oxazolinones.

Japanese Patent Application No 08-27132 refers to the preparation of certain oxazolones.

15 Giardina *et al.*, J. Med. Chem. **1996**, 39, 4602-4607 refer to the synthesis of cyclazosin enantiomers and their activity as  $\alpha_{1B}$ -antagonists.

Patane *et al.*, J. Med. Chem. **1998**, 41, 1205-1208 refer to L-765314 as a potent and selective  $\alpha_{1B}$ -antagonist.

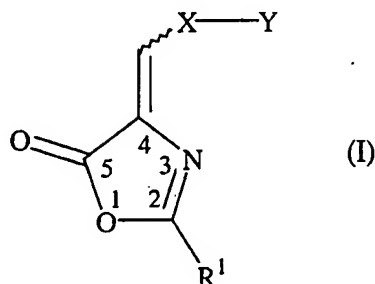
Xie *et al.*, Soc. for Neuroscience Abstract **24**, 2089(1998) refer to certain  
20  $\alpha_{1B}$ -adrenergic receptor mRNA expression in rat DRG after spinal nerve injury.

Lee *et al.*, J. Neurophysiol. **81**, 2226-2233 (1999) refer to certain receptor subtypes mediating the adrenergic sensitivity of pain behaviour.

25 Summary of the Invention

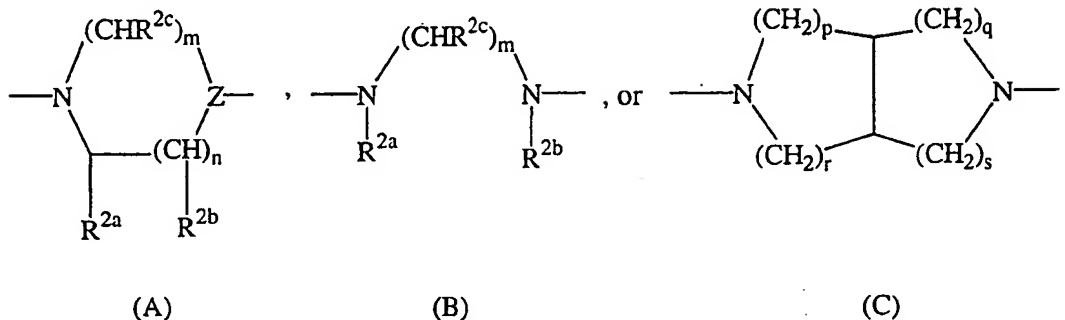
The present invention addresses the aforementioned needs in the art by providing oxazolone derivatives, and pharmaceutically acceptable salts or solvates thereof, which exhibit useful pharmacological properties. Particularly, the present invention relates to oxazolone derivatives, pharmaceutical  
30 compositions thereof and methods of using such derivatives as  $\alpha_1$ -adrenergic receptor ( $\alpha_1$ -adrenoceptor) modulators, preferably antagonists.

In one embodiment, the invention relates to a compound comprising the Formula (I):



wherein:

X is Formula (A), (B) or (C);



5

m is an integer ranging from 1 to 6 inclusive;

n is an integer ranging from 0 to 5 inclusive;

p, q, r and s are each independently integers ranging from 1 to 3 inclusive, with the proviso that when p is greater than one, r is 1 and when s is greater than one, q is 1;

10

Y is  $-(CH_2)_w-R^3$ ,  $-(CH_2)_w-CO-R^4$ ,  $-(CH_2)_w-CO-NH-R^5$ ,  $-(CH_2)_w-C(NR^6)-NH-R^7$ ,  $-(CH_2)_w-SO_2-R^8$ ,  $-(CH_2)_w-NH-R^9$ ,  $-(CH_2)_w-NH-CO-R^{10}$ ,  $-(CH_2)_w-NH-CO-NH-R^{11}$ , or  $-(CH_2)_w-NH-SO_2-R^{12}$ ; wherein w is an integer ranging from 0 to 3 inclusive;

15

Z is CH or N;

R¹ is cycloalkyl, cycloalkenyl, heterocyclic, aryl or heteroaryl;

R²ᵃ, R²ᵇ or R²ᶜ are each independently in each occurrence hydrogen, alkyl, alkenyl, cycloalkyl, aryl, or arylalkyl; or R²ᵃ and R²ᵇ taken together with the carbons to which they are attached form a 5- to 7-membered ring structure;

- 5 -

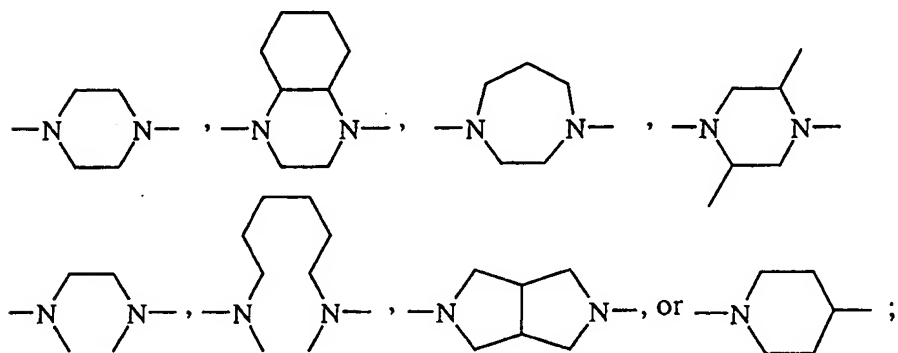
$R^3$  is heterocyclic or heteroaryl;

$R^4$ ,  $R^5$ ,  $R^8$ ,  $R^9$ ,  $R^{10}$ ,  $R^{11}$  and  $R^{12}$  are each independently in each occurrence hydrogen, alkyl, alkoxy, hydroxyalkyl, alkylthio, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocyclic, heterocyclicalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl;

$R^6$  and  $R^7$  are each independently in each occurrence hydrogen, alkyl, hydroxyalkyl, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocyclic, heterocyclicalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl;

or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof.

In a preferred embodiment, X is:



or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof.

In a more preferred embodiment, X is piperazinyl or piperidinyl; or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof. Even more preferably X is piperazinyl; or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof.

In a preferred embodiment, Y is  $-(CH_2)_w-R^3$ ,  $-(CH_2)_w-CO-R^4$ ,  $-(CH_2)_w-CO-NH-R^5$ ,  $-(CH_2)_w-C(NR^6)-NH-R^7$ ,  $-(CH_2)_w-SO_2-R^8$ ,  $-(CH_2)_w-NH-R^9$ ,  $-(CH_2)_w-NH-CO-R^{10}$ ,  $-(CH_2)_w-NH-CO-NH-R^{11}$ , or  $-(CH_2)_w-NH-SO_2-R^{12}$ ; or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof.

In another preferred embodiment, Y is  $-(CH_2)_w-CO-R^4$ ,  $-(CH_2)_w-SO_2-R^8$ ,  $-(CH_2)_w-NH-R^9$ ,  $-(CH_2)_w-NH-CO-R^{10}$ ,  $-(CH_2)_w-NH-CO-NH-R^{11}$ , or  $-(CH_2)_w-NH-SO_2-R^{12}$ ; or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof.

5 In another preferred embodiment, Y is  $-(CH_2)_w-R^3$ ; or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof.

In another preferred embodiment, Y is  $-(CH_2)_w-CO-NH-R^5$ ; or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically  
10 acceptable salts or solvates thereof.

In another preferred embodiment, Y is  $-(CH_2)_w-C(NR^6)-NH-R^7$ ; or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof.

In another preferred embodiment,  $R^1$  is aryl or heteroaryl; more preferably  
15  $R^1$  is an alkyl-, halo- or alkoxy-substituted phenyl, a bicyclic aryl or a bicyclic heteroaryl; and even more preferably  $R^1$  is a 3-substituted phenyl (e.g., 3-methylphenyl, 3-chlorophenyl, 3-methoxyphenyl), naphthyl, fluoronaphthyl, thianaphthenyl (benzothiophenyl), benzofuranyl, quinolinyl, indolyl, fluorobenzofuranyl, or benzimidazolyl; or individual isomers or racemic or non-  
20 racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof.

In another preferred embodiment,  $R^3$  is a moiety selected from benzooxazolyl, pyrazolyl, pyrimidyl, pyrrolyl, quinolinyl, isoquinolinyl, benzoisoquinolinyl dione, indolyl, imidazolyl, benzimidazolyl, imidazopyridinyl,  
25 oxazolyl, isooxazolyl, quinoxanilyl, thiazolyl, benzothiazolyl, or thiazolidinyl; wherein the moiety is optionally substituted with one or more of the following substituents: hydroxy, cyano, alkyl, alkoxy, thioalkyl, halo, haloalkyl, trifluoromethyl, hydroxyalkyl, alkoxycarbonyl, nitro, amino, alkylamino, dialkylamino, cycloalkyl, cycloalkylenyl, heterocyclic, aryl or heteroaryl; or  
30 individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof.

In another preferred embodiment, R<sup>4</sup> is alkyl, alkoxy, cycloalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl; or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof.

5 In another preferred embodiment, R<sup>5</sup> is alkyl, cycloalkyl, heterocyclicalkyl, aryl, arylalkyl, or heteroaryl; or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof.

In another preferred embodiment, R<sup>6</sup> is hydrogen or alkyl; or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically  
10 acceptable salts or solvates thereof.

In another preferred embodiment, R<sup>7</sup> is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, or heteroaryl; or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof.

In another preferred embodiment, R<sup>8</sup> is alkyl, aryl, arylalkyl, or heteroaryl;  
15 or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof.

In another preferred embodiment, R<sup>9</sup> is alkyl, arylalkyl, or heteroarylalkyl; or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof.

20 In another preferred embodiment, R<sup>10</sup> is alkyl, alkoxy, cycloalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl; or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof.

In another preferred embodiment, R<sup>11</sup> is alkyl, cycloalkyl, heterocyclicalkyl,  
25 aryl, arylalkyl, or heteroaryl; or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof.

In another preferred embodiment, R<sup>12</sup> is alkyl, aryl, arylalkyl, or heteroaryl; or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof.

30 In an additional embodiment, the invention relates to a pharmaceutical composition comprising a therapeutically effective amount of at least one compound of Formula (I), or individual isomers or racemic or non-racemic

mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof as described herein. In another embodiment, at least one compound of Formula (I), or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof as described herein, is an  
5 alpha<sub>1</sub>-adrenoceptor modulator. In a preferred embodiment at least one compound is an alpha<sub>1</sub>-adrenoceptor antagonist. In a more preferred embodiment, at least one compound of Formula (I), or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof as described herein is an alpha<sub>1B</sub>-adrenoceptor  
10 antagonist.

In another embodiment, the invention relates to a method of treating a disease state alleviable by treatment with an alpha<sub>1</sub>-adrenoceptor modulator. In a preferred embodiment, the invention relates to a method of treating a disease state alleviable by treatment with an alpha<sub>1</sub>-adrenoceptor antagonist, such as  
15 disease states of the urinary tract such as incontinence, benign prostatic hypertrophy, prostatitis, detrusor hyperreflexia, urinary frequency, nocturia, urinary urgency, overactive bladder, pelvic hypersensitivity (including interstitial cystitis, prostatitis, pelvic pain syndrome, infectious cystitis, prostatodynia, and the like), urge incontinence, urethritis, or idiopathic bladder hypersensitivity; male  
20 erectile dysfunction and female sexual dysfunction; pain including acute pain, inflammatory pain, neuropathic pain and complex regional pain syndromes; hypertension and cardiac dysfunctions resulting from altered contractility, and/or hypertrophy.

In a preferred embodiment, the disease state comprises disorders of the  
25 urinary tract, preferably the disease state is incontinence, benign prostatic hypertrophy, prostatitis, detrusor hyperreflexia, urinary frequency, nocturia, urinary urgency, overactive bladder, pelvic hypersensitivity, urge incontinence, urethritis, prostatodynia, cystitis or idiopathic bladder hypersensitivity.

In a preferred embodiment, the disease state is male erectile dysfunction  
30 or female sexual dysfunction.

In another preferred embodiment, the disease state is pain, preferably inflammatory pain, neuropathic pain, cancer pain, acute pain, chronic pain or complex regional pain syndromes.

In an additional embodiment, the invention provides a screening method for  
5 identifying a compound that modulates  $\alpha_{1B}$ -adrenergic receptor activity, comprising:

(a) measuring the activity of a test compound in a first binding assay,  
comprising

- (i) providing a preparation of a cell that expresses an  $\alpha_{1B}$ -adrenergic receptor,
- 10 (ii) combining the test compound with the cell preparation,
- (iii) measuring binding of the test compound to the cell preparation or the receptor; and

(b) measuring activity of the test compound in at least one pain model, preferably an animal pain model such as a tail flick model, a rat tail immersion  
15 model, a carrageenan-induced paw hyperalgesia model, a formalin behavior response model, a von Frey filament test, a radiant heat model, or a cold allodynia model

wherein (a) and (b) are done concurrently or consecutively in any order.

The said method may comprise a further step wherein

20 (c) the activity of the test compound is measured in a second binding assay, comprising

- (i) providing a preparation of a cell that expresses an  $\alpha_{1A}$ -adrenergic receptor, a preparation of a cell that expresses an  $\alpha_{1D}$ -adrenergic receptor, or a preparation of a cell that expresses an  $\alpha_{1A}$ -  
25 adrenergic receptor and a preparation of a cell that expresses an  $\alpha_{1D}$ -adrenergic receptor,
- (ii) combining the test compound with the cell preparation, and
- (iii) measuring the binding of the test compound to the cell or the receptor;

30 wherein (a), (b) and (c) are done concurrently or consecutively in any order.



In the above methods the preparation of the cell that expresses the  $\alpha_{1A}$ -adrenergic receptor or the  $\alpha_{1B}$ -adrenergic receptor is preferably a membrane preparation or an intact cell preparation.

The above methods may further comprise measuring the effect of the test  
5 compound on general locomotor activity; or measuring the effect of the test compound on sedation; or measuring a functional  $\alpha_1$ -adrenergic receptor activity of the test compound, e.g. in an in vitro test or an in vivo test.

The invention relates also to the compounds obtained by said screening method, as well as to pharmaceutical compositions, comprising a therapeutically  
10 effective amount of a compound identified by the said screening method, or a pharmaceutically acceptable salt or hydrate of said compound, and one or more pharmaceutically acceptable additives, diluents, or carriers.

In an additional embodiment, the invention relates to a method of treating a subject which comprises administering to the subject a therapeutically effective  
15 amount of at least one compound obtained by the above screening method or at least one compound of Formula (I), or individual isomers or racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof as described herein or a pharmaceutical composition thereof as described herein. In a preferred embodiment, the subject has a disease state  
20 alleviable by treatment with an  $\alpha_1$ -subtype adrenoceptor modulator, preferably an antagonist, more preferably an  $\alpha_{1B}$ -adrenoceptor antagonist.

These and other embodiments of the present invention will readily occur to those of ordinary skill in the art in view of the disclosure herein.

## 25 Detailed Description

The practice of the present invention will employ, unless otherwise indicated, conventional methods of chemistry, biochemistry and pharmacology, within the skill of the art. Such techniques are explained fully in the literature. See, e.g., *Remington's Pharmaceutical Sciences*, 19th Edition (Easton,  
30 Pennsylvania: Mack Publishing Company, 1995); *Methods In Enzymology* (S. Colowick and N. Kaplan, eds., Academic Press, Inc.); *Textbook of Pain* (P.D.

Wall and R. Melzack, editors, Third Edition, Churchill Livingstone, 1994); *Fieser and Fieser's Reagents for Organic Synthesis*, Wiley & Sons, New York, 1991, Volumes 1-15; *Rodd's Chemistry of Carbon Compounds*, Elsevier Science Publishers, 1989, Volumes 1-5 and Supplementals; and *Organic Reactions*,  
5 Wiley & Sons, New York, 1991, Volumes 1-40.

All publications, patents and patent applications cited herein, whether *supra* or *infra*, are hereby each incorporated by reference in their entirety.

As used in this specification and the appended claims, the singular forms "a," "an" and "the" include singular and plural references unless the content  
10 clearly dictates otherwise. Thus, for example, reference to "an antagonist" may include a mixture of two or more such agents.

### I. Definitions

In describing the present invention, the following terms will be employed,  
15 and are intended to be defined as indicated below.

"Alkyl" means the monovalent linear or branched saturated hydrocarbon radical, consisting solely of carbon and hydrogen atoms, having from one to twelve carbon atoms inclusive, unless otherwise indicated. Examples of an alkyl radical include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, n-hexyl, octyl, dodecyl, and the like.  
20

"Lower alkyl" means the monovalent alkyl radical as defined herein, having from one to six carbon atoms inclusive, unless otherwise indicated. Examples of a lower alkyl radical include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl, pentyl, n-hexyl and the like.

25 "Alkylene" means the divalent linear or branched saturated hydrocarbon radical consisting solely of carbon and hydrogen atoms, containing no unsaturation and having from one to six carbons inclusive, unless otherwise indicated. Examples of alkylene radicals include, but are not limited to, methylene, ethylene, propylene, 2-methyl-propylene, butylene, 2-ethylbutylene,  
30 and the like.

"Alkenyl" means the monovalent linear or branched unsaturated hydrocarbon radical, consisting solely of carbon and hydrogen atoms, containing

a double bond and having from two to six carbon atoms inclusive, unless otherwise indicated. Examples of an alkenyl radical include, but are not limited to, ethenyl, allyl, 1-propenyl, 2-butenyl, and the like.

“Alkynyl” means the monovalent linear or branched unsaturated hydrocarbon radical, consisting solely of carbon and hydrogen atoms, containing a triple bond and having from two to six carbon atoms inclusive, unless otherwise indicated. Examples of an alkynyl radical include, but are not limited to, ethynyl, 1-propynyl, 2-butyne, and the like.

“Alkoxy” means the radical -O-R, wherein R is a lower alkyl radical as defined herein. Examples of an alkoxy radical include, but are not limited to, methoxy, ethoxy, isopropoxy, and the like.

“Alkoxycarbonyl” means the radical R-O-C(O)-, wherein R is a lower alkyl radical as defined herein. Examples of an alkoxycarbonyl radical include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, sec-butoxycarbonyl, and the like.

“Acyloxy” means the radical -OC(O)R, wherein R is a lower alkyl radical as defined herein. Examples of acyloxy radicals include, but are not limited to, acetoxy, propionyloxy, and the like.

“Acyl” or “alkanoyl” means the radical -C(O)-R wherein R is a lower alkyl radical as defined herein. Examples of acyl radicals include, but are not limited to, formyl, acetyl, propionyl, butyryl, and the like.

“Alkylamino” means the radical -NHR, wherein R is a lower alkyl radical as defined herein. Examples of alkylamino radicals include, but are not limited to, methylamino, (1-ethylethyl)amino, and the like.

“Aminoalkyl” means the radical -RNR'R", wherein R is a lower alkyl radical as defined herein, and R' and R" are each independently H or a lower alkyl radical as defined herein. Examples of aminoalkyl radicals include, but are not limited to, aminomethyl, aminoethyl, aminopropyl, and the like.

“Alkylthio” means the radical -SR, wherein R is a lower alkyl radical as defined herein. Examples of alkylthio radicals include, but are not limited to, methylthio, butylthio, and the like.

"Dialkylamino" means the radical -NR'R", wherein R' and R" are each independently lower alkyl radicals as defined herein. Examples of dialkylamino radicals include, but are not limited to, dimethylamino, methylethylamino, diethylamino, di(1-methylethyl)amino, and the like.

5 "Aryl" means the monovalent monocyclic aromatic hydrocarbon radical consisting of one or more fused rings in which at least one ring is aromatic in nature, which can optionally be substituted with one or more of the following substituents: hydroxy, cyano, alkyl, alkoxy, thioalkyl, halo, haloalkyl, trifluoromethyl, hydroxyalkyl, alkoxycarbonyl, nitro, amino, alkylamino, 10 dialkylamino, aminocarbonyl, carbonylamino, aminosulfonyl and sulfonylamino, unless otherwise indicated. Examples of aryl radicals include, but are not limited to, phenyl, naphthyl, biphenyl, diphenylmethyl, 9H-fluorenyl, indanyl, anthraquinolyl, and the like.

"Heteroaryl" means the monovalent aromatic carbocyclic radical having 15 one or more rings incorporating one, two, or three heteroatoms within the ring (chosen from nitrogen, oxygen, or sulfur) which can optionally be substituted with one or more of the following substituents: hydroxy, cyano, alkyl, alkoxy, thioalkyl, halo, haloalkyl, trifluoromethyl, hydroxyalkyl, alkoxycarbonyl, nitro, amino, alkylamino, dialkylamino, aminocarbonyl, carbonylamino, aminosulfonyl and 20 sulfonylamino, unless otherwise indicated. Examples of heteroaryl radicals include, but are not limited to, naphthyridinyl, anthranilyl, benzooxazolyl, pyridyl, pyrrolyl, pyrazolyl, pyrazinyl, pyrimidyl, thiophenyl, furanyl, benzofuranyl, dihydrobenzofuranyl, 3,3-dimethyl-2,3-dihydrobenzofuranyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 25 1,2,3,4-tetrahydroisoquinolinyl, tetrahydroquinoxalyl, benzodioxazolyl, benzoisoquinolinyl dione, benzodioxanyl, indolyl, 2,3-dihydroindolyl, thianaphthenyl, dihydrothianaphthenyl, imidazolyl, benzoimidazolyl, benzimidazolyl, azabenzimidazolyl, oxazolyl, isooxazolyl, quinoxalyl, thiazolyl, benzothiazolyl, thiazolidinyl, pyranyl, tetrahydropyranyl pyranyl, 30 benzo[1,3]dioxolyl, 2,3-dihydrobenzo[1,4]dioxinyl, thienyl, benzo[b]thienyl, 1,2,3,4-tetrahydro[1,5]naphthyridinyl, 2H-3,4-dihydrobenzo[1,4]oxazine, 4,5-dihydro-1H-imidazol-2-yl, and the like.

"Arylalkyl" means the radical R'R"-, wherein R' is an aryl or heteroaryl radical as defined herein, and R" is an alkyl radical as defined herein. Examples of arylalkyl radicals include, but are not limited to, benzyl, phenylethyl, 3-phenylpropyl, and the like.

5 "Cycloalkyl" means the monovalent saturated carbocyclic radical consisting of one or more rings, which can optionally be substituted with one or more of the following substituents: hydroxy, cyano, alkyl, alkoxy, thioalkyl, halo, haloalkyl, trifluoromethyl, hydroxyalkyl, alkoxycarbonyl, nitro, amino, alkylamino, dialkylamino, aminocarbonyl, carbonylamino, aminosulfonyl and sulfonylamino,  
10 unless otherwise indicated. Examples of cycloalkyl radicals include, but are not limited to, cyclopropyl, cyclobutyl, 3-ethylcyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, hydrogenated derivatives of aryl as defined herein, and the like.

"Cycloalkylalkyl" means the radical R'R"-, wherein R' is a cycloalkyl radical as defined herein and R" is an alkyl radical as defined herein. Examples  
15 of cycloalkylalkyl radicals include, but are not limited to, cyclopropylmethyl, cyclohexylmethyl, 3-ethylcyclobutyl, cyclopentylethyl, and the like.

"Cycloalkenyl" means the monovalent unsaturated carbocyclic radical consisting of one or more rings, which can optionally be substituted with one or more of the following substituents: hydroxy, cyano, alkyl, alkoxy, thioalkyl, halo,  
20 haloalkyl, trifluoromethyl, hydroxyalkyl, alkoxycarbonyl, nitro, amino, alkylamino, dialkylamino, aminocarbonyl, carbonylamino, aminosulfonyl and sulfonylamino, unless otherwise indicated. Examples of cycloalkenyl radicals include, but are not limited to, cyclopentenyl, cyclohexenyl, cycloheptenyl, hydrogenated derivatives of aryl as defined herein, and the like.

25 "Heterocyclyl" means the monovalent saturated carbocyclic radical, consisting of one or more rings, incorporating one, two or three heteroatoms (chosen from nitrogen, oxygen or sulfur), which can optionally be substituted with one or more of the following substituents: hydroxy, cyano, alkyl, alkoxy, thioalkyl, halo, haloalkyl, trifluoromethyl, hydroxyalkyl, alkoxycarbonyl, nitro, amino,  
30 alkylamino, dialkylamino, aminocarbonyl, carbonylamino, aminosulfonyl and sulfonylamino, unless otherwise indicated. Examples of heterocyclic radicals include, but are not limited to, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl,

piperazinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, imidazolidinyl, pyrrolidinyl, pyrrolidin-2-one, pyrrolidin-2,3-dione, hydrogenated derivatives of heteroaryl as defined herein, and the like.

“Heterocycloalkyl” means the radical of the formula  $R'R$ , where  $R'$  is a  
5 heterocyclic radical as defined herein and  $R$  is an alkylene radical as defined herein. Examples of heterocycloalkyl radicals include, but are not limited to, 1-piperazinylmethyl, 2-morpholinomethyl, and the like.

“Halogen” means the radical fluoro, chloro, bromo, and iodo.

“Haloalkyl” means the lower alkyl radical as defined herein substituted in  
10 any position with one or more halogen atoms as defined herein. Examples of haloalkyl radicals include, but are not limited to, 1,2-difluoropropyl, 1,2-dichloropropyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, and the like.

“Hydroxyalkyl” means the lower alkyl radical as defined herein, substituted  
15 with one or more hydroxy groups. Examples of hydroxyalkyl radicals include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 1-(hydroxymethyl)-2-hydroxyethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl, and 2-(hydroxymethyl)-3-hydroxypropyl, and the like.

20 “Optional” or “optionally” means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase “which group is optionally substituted with one to three halo atoms” or “optionally substituted aryl” means that the group referred to  
25 may or may not be substituted in order to fall within the scope of the invention, and that the description includes both substituted and unsubstituted moieties.

“Protected” in reference to a compound or a group means the derivative of compound or group in which a reactive site or sites are blocked with protective groups.

30 “Protective group” or “protecting group” means the group which selectively blocks one reactive site in a multifunctional compound such that a chemical reaction can be carried out selectively at another unprotective reactive site and

which can be readily removed after the selective reaction is completed. Certain processes may rely upon the protective groups to block reactive oxygen or nitrogen atoms present in the reactants. Acceptable protective groups for alcoholic or phenolic hydroxyl groups, which may be removed successively and  
5 selectively includes groups protected as acetates, haloalkyl carbonates, benzyl ethers, alkylsilyl ethers, heterocyclic ethers, and methyl or alkyl ethers, and the like. Protective or blocking groups for carboxyl groups are similar to those described for hydroxyl groups, preferably *tert*-butyl, benzyl or methyl esters.

"Amino-protecting group" means the protecting group that refers to those  
10 organic groups intended to protect the nitrogen atom against undesirable reactions during synthetic procedures and includes, but is not limited to benzyl, benzyloxycarbonyl (carbobenzyloxy; CBZ), *p*-methoxybenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl, *tert*-butoxycarbonyl (BOC), trifluoroacetyl, and the like. It is preferred to use either BOC or CBZ as the amino-protecting group because  
15 of the relative ease of removal, for example by mild acids in the case of BOC, *e.g.*, trifluoroacetic acid or hydrochloric acid in ethyl acetate; or by catalytic hydrogenation in the case of CBZ.

"Hydroxy-protecting group" means the protecting group that preserves a hydroxy group that otherwise would be modified by certain chemical reactions.  
20 Suitable hydroxy-protecting groups include ether-forming groups that can be removed easily after completion of all other reaction steps, such as the benzyl or the trityl group optionally substituted in their phenyl ring. Other suitable hydroxy-protecting groups include alkyl ether groups, the tetrahydropyranyl, silyl, trialkylsilyl ether groups and the allyl group.

25 "Deprotection" or "deprotecting" means the process by which a protective group is removed after the selective reaction is completed. Certain protective groups may be preferred over others due to their convenience or relative ease of removal. Deprotecting reagents for protected hydroxyl or carboxyl groups include potassium or sodium carbonates, lithium hydroxide in alcoholic solutions,  
30 zinc in methanol, acetic acid, trifluoroacetic acid, palladium catalysts, or boron tribromide, and the like.

"Leaving group" means the group with the meaning conventionally associated with it in synthetic organic chemistry, i.e., an atom or group displaceable under alkylating conditions. Examples of leaving groups include, but are not limited to, halogen, alkane- or arenesulfonyloxy, such as

5 methanesulfonyloxy, ethanesulfonyloxy, benzenesulfonyloxy, tosyloxy, thiomethyl, and thienyloxy, dihalophosphinoyloxy, tetrahalophosphoxy, optionally substituted benzyloxy, isopropoxy, mesyloxy, tosyloxy, acyloxy, and the like.

"Inert organic solvent" or "inert solvent" means the solvent inert under the conditions of the reaction being described in conjunction therewith including, for

10 example, benzene, toluene, acetonitrile, methyl sulfoxide (DMSO), tetrahydrofuran (THF), N,N-dimethylformamide (DMF), chloroform ( $\text{CHCl}_3$ ), methylene chloride or dichloromethane ( $\text{CH}_2\text{Cl}_2$ ), dichloroethane, diethyl ether, ethyl acetate, acetone, methylethyl ketone, methanol, ethanol, propanol, isopropanol, *tert*-butanol, dioxane, pyridine, and the like. Unless specified to the

15 contrary, the solvents used in the reactions of the present invention are inert solvents.

"Isomerism" means the compounds have identical molecular formulae but that differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of

20 their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes optical isomers. A carbon atom bonded to four nonidentical substituents is termed a "chiral center."

25 "Chiral isomer" means a compound with one chiral center. It has two enantiomeric forms of opposite chirality, and may exist as either an individual enantiomer or as a mixture of enantiomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a "racemic mixture." A compound that has more than one chiral center has  $2^{n-1}$

30 enantiomeric pairs, where n is the number of chiral centers. Compounds with more than one chiral center may exist as either an individual diastereomer or as a mixture of diastereomers, termed a "diastereomeric mixture."



When one chiral center is present a stereoisomer may be characterized by the absolute configuration (R or S) of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under  
5 consideration are ranked in accordance with the Sequence Rule of Cahn, Ingold and Prelog. (Cahn et al. *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511; Cahn et al. *Angew. Chem.* 1966, 78, 413; Cahn and Ingold *J. Chem. Soc.* (London) 1951, 612; Cahn et al. *Experientia* 1956, 12, 81; Cahn, *J. Chem. Educ.* 1964, 41, 116).

10 "Geometric isomers" means the diastereomers that owe their existence to hindered rotation about double bonds. These configurations are differentiated in their names by prefixes cis and trans, or Z and E, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

15 "Atropic isomers" means the isomers owing their existence to restricted rotation caused by hindrance of rotation of large groups about a central bond.

The scope of the present invention comprises compounds that possess geometric isomerism, and that may or may not possess chiral or atropic isomerism in their substituents. Such compounds can therefore be produced as  
20 mixtures of stereoisomers, or as the individual isolated or purified stereoisomers. The individual enantiomers may be obtained by resolving a racemic or non-racemic mixture of an intermediate at some appropriate stage of the synthesis followed by completion of the synthesis in a way that preserves chirality, or by resolution of the compound of Formula (I) by conventional means.  
25 The individual enantiomers as well as racemic or non-racemic mixtures thereof are encompassed within the scope of the present invention, all of which are intended to be depicted by the structures of this specification unless otherwise specifically indicated.

A "pharmaceutically acceptable carrier" means a carrier that is useful in  
30 preparing a pharmaceutical composition that is generally compatible with the other ingredients of the composition, not deleterious to the recipient, and neither biologically nor otherwise undesirable, and includes a carrier that is acceptable

for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable carrier" as used in the specification and claims includes both one and more than one such carrier.

A "pharmaceutically acceptable salt" of a compound means a salt that is  
5 pharmaceutically acceptable, as described herein, and that possesses the desired pharmacological activity of the parent compound. Such salts include:

(1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, benzenesulfonic  
10 acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, camphorsulfonic acid, p-chlorobenzenesulfonic acid, cinnamic acid, citric acid, cyclopentanepropionic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, hexanoic acid, heptanoic acid, hydroxynaphthoic acid, 2-hydroxyethanesulfonic acid, lactic acid, lauryl sulfuric  
15 acid, malic acid, maleic acid, malonic acid, mandelic acid, methanesulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), muconic acid, 2-naphthalenesulfonic acid, oxalic acid, 3-phenylpropionic acid, propionic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, tartaric acid, trimethylacetic acid, tertiary butylacetic acid,  
20 p-toluenesulfonic acid, and the like; or

(2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic or inorganic base. Acceptable  
organic bases include diethanolamine, ethanolamine, N-methyl-glucamine,  
25 triethanolamine, tromethamine, and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, and sodium hydroxide.

The preferred pharmaceutically acceptable salts are the salts formed from acetic acid, hydrochloric acid, sulphuric acid, methanesulfonic acid, maleic acid,  
30 phosphoric acid, tartaric acid, citric acid, sodium, potassium, calcium, zinc, and magnesium.

It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same acid addition salt

"Crystal forms" (or polymorphs) means crystal structures in which a  
5 compound can crystallize in different crystal packing arrangements, all of which have the same elemental composition. Different crystal forms usually have different X-ray diffraction patterns, infrared spectra, melting points, density hardness, crystal shape, optical and electrical properties, stability and solubility. Recrystallization solvent, rate of crystallization, storage temperature, and other  
10 factors may cause one crystal form to dominate

"Solvates" means solvent additions forms that contain either stoichiometric or non stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate, when  
15 the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one of the substances in which the water retains its molecular state as H<sub>2</sub>O, such combination being able to form one or more hydrate.

A "therapeutically effective amount" means an amount of a compound  
20 that, when administered to a subject for treating a disease state, is sufficient to effect such treatment for the disease state. The "therapeutically effective amount" will vary depending on the compound, and disease state being treated, the severity of the disease state treated, the age and relative health of the subject, the route and form of administration, the judgement of the attending  
25 medical or veterinary practitioner, and other factors.

"Prodrug" means a pharmacologically inactive form of a compound which must be metabolized in vivo, e.g., by biological fluids or enzymes, by a subject after administration into a pharmacologically active form of the compound in order to produce the desired pharmacological effect. The prodrug can be  
30 metabolized before absorption, during absorption, after absorption, or at a specific site. Although metabolism occurs for many compounds primarily in the liver, almost all other tissues and organs, especially the lung, are able to carry

out varying degrees of metabolism. Prodrug forms of compounds may be utilized, for example, to improve bioavailability, improve subject acceptability such as by masking or reducing unpleasant characteristics such as bitter taste or gastrointestinal irritability, alter solubility such as for intravenous use, provide for  
5 prolonged or sustained release or delivery, improve easy of formulation, or provide site-specific delivery of the compound. Reference to a compound herein includes prodrug forms of a compound.

"Disease state" means any disease, condition, symptom, or indication.

"Modulator" means a molecule, such as a compound, that interacts with a  
10 target. The interactions include, but are not limited to, agonist, antagonist, and the like, as defined herein.

"Antagonist" means a molecule such as a compound, a drug, an enzyme inhibitor, or a hormone, that diminishes or prevents the action of another molecule or receptor site.

15 "Agonist" means a molecule, such as a compound, a drug, an enzyme activator or a hormone, that enhances the activity of another molecule or receptor site.

"Alpha<sub>1</sub>-adrenergic receptors", "alpha<sub>1A</sub>-adrenergic receptors" (previously known as "alpha<sub>1C</sub>-adrenergic receptors"), "alpha<sub>1B</sub>-adrenergic receptors",  
20 "alpha<sub>1D</sub>-adrenergic receptors", or "alpha<sub>1L</sub>-adrenergic receptors", used interchangeably with "alpha<sub>1</sub>-adrenoceptors", "alpha<sub>1A</sub>-adrenoceptors" (previously known as "alpha<sub>1C</sub>-adrenoceptors"), "alpha<sub>1B</sub>-adrenoceptors", "alpha<sub>1D</sub>-adrenoceptors", and "alpha<sub>1L</sub>-adrenoceptors", respectively, refers to a molecule conforming to the seven membrane-spanning G-protein receptors, which under  
25 physiologic conditions mediate various actions, for example, in the central and/or peripheral sympathetic nervous system through the binding of the catecholamines, epinephrine, and norepinephrine. Examples of physiological effects mediated by "alpha<sub>1</sub>-adrenoceptors" include, but are not limited to, control of blood pressure, glycogenolysis, growth and hypertrophy of cardiac myocytes,  
30 contractility of the urinary tract, and the like.

The term "alpha<sub>1</sub>-adrenergic receptor subtype" used interchangeably with "alpha<sub>1</sub>-adrenoceptor subtype" refers to a distinct member of the class of alpha<sub>1</sub>-

adrenoceptors, selected from the  $\alpha_{1A}$ - (previously known as  $\alpha_{1C}$ -),  $\alpha_{1B}$ -,  $\alpha_{1D}$ - and  $\alpha_{1L}$ -adrenoceptors. The subtypes have been distinguished based on differential binding profiles of ligands, such as the agonist oxymetazoline, and such as the antagonists, WB4101 and phentolamine.

5 Furthermore, the genes encoding the  $\alpha_{1A}$ - (previously known as  $\alpha_{1C}$ -),  $\alpha_{1B}$ - and  $\alpha_{1D}$ -subtypes have been isolated and cloned. The existence of an additional subtype, the  $\alpha_{1L}$ -adrenergic receptor subtype, has been proposed; however, the gene for the  $\alpha_{1L}$ -adrenergic receptor subtype has not yet been cloned.

10 The term "specific  $\alpha_1$ -adrenergic receptor" as used herein, refers to a distinct member of the group or class of adrenoceptors, which may be selected from the  $\alpha_{1A}$ - (previously known as  $\alpha_{1C}$ -),  $\alpha_{1B}$ -,  $\alpha_{1D}$ - and  $\alpha_{1L}$ -adrenoceptors. Preferred species from which may be derived or isolated  $\alpha_1$ -adrenergic receptor subtype polypeptides, genes encoding an  $\alpha_1$ -adrenergic  
15 receptor subtype, and/or cells, tissues and organs that express one or more  $\alpha_1$ -adrenergic receptor subtype, include human, bovine, rat, murine, porcine, bovine, and the like. A more preferred species is human.

Examples of cell lines that are available from the American Type Culture Collection (ATCC) that express human receptors as follows (ATCC Accession No.):  
20  $\alpha_{1A}$  (CRL 11138),  $\alpha_{1B}$  (CRL 11139),  $\alpha_{1C}$  (CRL 11140),  $\alpha_{2A}$  (CRL 11180),  $\alpha_{2B}$  (CRL 10275, CRL 11888),  $\alpha_{2C}$  (CRL 11181), 5-HT<sub>1D1</sub> (CRL 10421), 5-HT<sub>1D2</sub> (CRL 10422), 5-HT<sub>1E</sub> (CRL 10913), 5-HT<sub>1F</sub> (CRL 10957), 5-HT<sub>4B</sub> (CRL 11166), 5-HT<sub>1A</sub> (CRL 11889) and 5-HT<sub>2</sub> (CRL 10287).

In addition, plasmids are available from the ATCC that harbor cloned human  
25 D2, H2 and H1 receptors (ATCC Accession Nos. 7534, 75345 and 75346, respectively) that can be used to transfect cells using conventional methods well known in the art to provide cells that express on their surface the receptor of interest. Transient transfection of COS-7 cells with a plasmid can be performed using any method known in the art, e.g., the DEAE-dextran method. Briefly, a plasmid  
30 comprising an expression vector for the receptor of interest is added to monolayers of COS-7 cells bathed in DEAE-dextran solution. To enhance the efficiency of

transfection, dimethyl sulfoxide can be added (Lopata et al. (1984) *Nucleic Acids Res.* 12:5707-5717). Cells are then grown under controlled conditions and used in experiments after about 72 hours. Stable cells lines can also be obtained by methods well known in the art. For example, a suitable host cell can be cotransfected using, e.g., the calcium phosphate method, with a plasmid comprising an expression vector for the receptor of interest and a plasmid comprising a gene that allows for selection of successfully transfected cells. Cells are then grown in a controlled environment and selected for expression of the receptor of interest. By continuing to grow and select cells stable, cell lines can be obtained expressing the receptor of interest.

Additional reference with respect to the preparation of DNA encoding these receptors and recombinant cells expressing the DNA can be made to U.S. Patent Nos. 5,610,174 to Craig et al., 5,556,753 and 5,714,381 to Bard et al., 5,155,218, 5,360,735, 5,476,782, 5,595,880, 5,639,652, 5,652,113, 5,786,155 and 5,786,157 to Weinshank et al., and 5,403,847, 5,578,611, and 5,780,485 to Gluchowski et al.

Binding Assays: The binding of a test compound to a receptor of interest can be detected by use of a radioligand selective for the receptor. Any radioligand binding technique known in the art may be used to detect the receptor (see, e.g., Winzor et al. (1995) *Quantitative Characterization of Ligand Binding*, Wiley-Liss, Inc., NY). Binding assays, the evaluation of analgesic activity of a test compound, and/or the evaluation of other functional  $\alpha_1$ -adrenergic receptor-mediated activity of a test compound, as described hereinbelow, can be carried out concurrently and/or consecutively, in any order.

The binding of a test compound to a receptor of interest can be evaluated by, e.g., competitive binding assays using membrane preparations derived from cells that express the receptor or, alternatively, intact cells that express the receptor can be used. First, conditions are determined that allow measurement of the specific binding of a compound known to bind to the receptor. Then, the binding of the known compound to the receptor in a membrane preparation or intact cell preparation is evaluated in the presence of several different concentrations of the test compound. Binding of the test compound to the receptor results in a diminution in the amount of the known compound that binds to the receptor. A test compound having a high

affinity for the receptor of interest displaces a given fraction of the bound known compound at a concentration lower than the concentration that would be required if the test compound has a low affinity for the receptor of interest. Thus, for example, competitive radioligand binding assays can be done using the following

- 5 radioligand/compound combinations for determining specific and nonspecific binding for receptors of interest: [ $^3\text{H}$ ]prazosin/phentolamine ( $\alpha_1$ ); [ $^3\text{H}$ ]rauwolscine/phentolamine ( $\alpha_2$ ); [ $^3\text{H}$ ]mepyramine/mepyramine ( $\text{H}_1$ ); [ $^3\text{H}$ ]tiotidine/histamine ( $\text{H}_2$ ); [ $^3\text{H}$ ]serotonin/serotonin ( $5\text{-HT}_1$ ); [ $^3\text{H}$ ]ketanserin/ mianserin ( $5\text{-HT}_2$ ); [ $^3\text{H}$ ]-8-OH-DPAT/mianserin ( $5\text{-H}_{1A}$ ); and [ $^3\text{H}$ ]spiperone/ (+)butaclamol ( $\text{D}_2$ ).

- 10 "Alpha $_{1B}$ -adrenergic receptors" means a specific alpha $_1$ -adrenoceptor expressed in numerous tissues, most notably in the liver, heart and cerebral cortex. alpha $_{1B}$ -adrenoceptors are also present in areas of the spinal cord which receive input from sympathetic neurons originating in the pontine micturition center, and are presumed to be involved in the regulation of bladder function.

- 15 The term "cell preparation" as used herein with respect to the expression of an  $\alpha_1$ -adrenergic receptor or an  $\alpha_1$ -adrenergic receptor subtype intends any form of a cell that expresses the receptor or receptor subtype of interest in which receptor- or receptor subtype-specific binding of a ligand, a radioligand, a test compound, or the like, can be measured. The term "cell preparation" includes, but is not limited to, a  
20 tissue explant, an intact cell isolated from a subject or tissue, an intact cultured or recombinant cell, as well as a disrupted cell, e.g., a cell membrane homogenate, a solubilized cell membrane in which receptor-specific binding can be measured, and the like.

- The term "pharmacological effect" as used herein encompasses effects  
25 produced in the subject that achieve the intended purpose of a therapy. In one preferred embodiment, a pharmacological effect means that pain symptoms of the subject being treated are prevented, alleviated, or reduced. For example, a pharmacological effect would be one that results in the reduction of pain in a treated subject. In another preferred embodiment, a pharmacological effect  
30 means that disorders or symptoms of the urinary tract of the subject being

treated are prevented, alleviated, or reduced. For example, a pharmacological effect would be one that results in the prevention or reduction of incontinence or pelvic hypersensitivity in a treated subject.

"Treating" or "treatment" of a disease state includes:

- 5 (1) preventing the disease state, i.e. causing the clinical symptoms of the disease state not to develop in a subject that may be exposed to or predisposed to the disease state, but does not yet experience or display symptoms of the disease state,
- (2) inhibiting the disease state, i.e., arresting the development of the  
10 disease state or its clinical symptoms, or
- (3) relieving the disease state i.e., causing regression of the disease state or its clinical symptoms.

The term "subject" as used herein encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, any member of  
15 the Mammalia class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds and the like. The  
20 term does not denote a particular age or sex.

"Trauma" means any wound or injury. Trauma can produce, for example, acute and/or chronic pain, inflammatory pain, and neuropathic pain.

"Pain" means the more or less localized sensation of discomfort, distress, or agony, resulting from the stimulation of specialized nerve endings. There are  
25 many types of pain, including, but not limited to, lightning pains, phantom pains, shooting pains, acute pain, inflammatory pain, neuropathic pain, complex regional pain, neuralgia, neuropathy, and the like (*Dorland's Illustrated Medical Dictionary*, 28th Edition, W.B. Saunders Company, Philadelphia, Pa). The goal of treatment of pain is to reduce the degree or severity of pain perceived by a  
30 treatment subject.

"Neuropathic pain" means the pain resulting from functional disturbances and/or pathological changes as well as noninflammatory lesions in the peripheral



nervous system. Examples of neuropathic pain include, but are not limited to, thermal or mechanical hyperalgesia, thermal or mechanical allodynia, diabetic pain, entrapment pain, and the like.

"Hyperalgesia" means the abnormally increased pain sense, such as pain  
5 that results from an excessive sensitiveness or sensitivity.

"Hypalgesia" (or "hypoalgesia") means the decreased pain sense.

"Allodynia" means the pain that results from a non-noxious stimulus to the skin. Examples of allodynia include, but are not limited to cold allodynia, tactile allodynia and the like.

10 "Complex regional pain syndromes" means the pain that includes, but is not limited to, reflex sympathetic dystrophy, causalgia, sympathetically maintained pain, and the like.

"Causalgia" means the burning pain, often accompanied by trophic skin changes, due to injury of a peripheral nerve.

15 "Nociception" means pain sense. "Nociceptor" means a structure that mediates nociception. Nociception may be the result of a physical stimulus, such as, mechanical, electrical, thermal, or a chemical stimulus. Most nociceptors are in either the skin or the viscera walls.

"Analgesia" means the relief of pain without the loss of consciousness. An  
20 "analgesic" is an agent or drug useful for relieving pain, again, without the loss of consciousness.

"Disorders of the urinary tract" or "uropathy" used interchangeably with "symptoms of the urinary tract" means the pathologic changes in the urinary tract. Symptoms of the urinary tract include overactive bladder (also known as  
25 detrusor hyperactivity), outlet obstruction, outlet insufficiency, and pelvic hypersensitivity. Examples of urinary tract disorders include, but are not limited to, incontinence, benign prostatic hypertrophy (BPH), prostatitis, detrusor hyperreflexia, outlet obstruction, urinary frequency, nocturia, urinary urgency, overactive bladder, pelvic hypersensitivity, urge incontinence, urethritis,  
30 prostatodynia, cystitis, idiopathic bladder hypersensitivity, and the like.

"Overactive bladder" or "Detrusor hyperactivity" includes, but is not limited to, the changes symptomatically manifested as urgency, frequency, reduced

bladder capacity, incontinence episodes, and the like; the changes urodynamically manifested as changes in bladder capacity, micturition threshold, unstable bladder contractions, sphincteric spasticity, and the like; and the symptoms usually manifested in detrusor hyperreflexia (neurogenic bladder), in  
5 conditions such as outlet obstruction, outlet insufficiency, pelvic hypersensitivity, or in idiopathic conditions such as detrusor instability, and the like.

"Outlet obstruction" includes, but is not limited to, benign prostatic hypertrophy (BPH), urethral stricture disease, tumors and the like. It is usually symptomatically manifested as obstructive (low flow rates, difficulty in initiating  
10 urination, and the like), and irritative (urinary urge and frequency, suprapubic pain, nocturia, and the like).

"Outlet insufficiency" includes, but is not limited to, urethral hypermobility, intrinsic sphincteric deficiency, or mixed incontinence. It is usually symptomatically manifested as stress incontinence.

15 "Pelvic Hypersensitivity" includes but is not limited to pelvic pain, interstitial (cell) cystitis, prostatic pain, prostatitis, vulvodynia, urethritis, orchialgia, and the like. It is symptomatically manifested as pain, inflammation or discomfort referred to the pelvic region, and usually includes symptoms of overactive bladder.

20

## II. Modes of Carrying out the Invention

Before describing the present invention in detail, it is to be understood that this invention is not limited to particular formulations or process parameters as such may, of course, vary. It is also to be understood that the terminology used  
25 herein is for the purpose of describing particular embodiments of the invention only, and is not intended to be limiting.

Although a number of methods and materials similar or equivalent to those described herein can be used in the practice of the present invention, the preferred materials and methods are described herein.

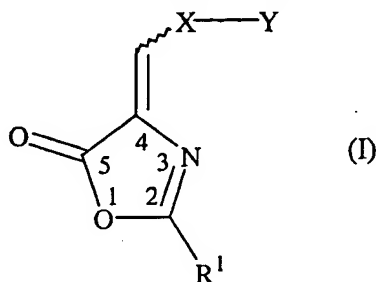
30

### Nomenclature

The naming and numbering of the compounds of this invention is illustrated below.

In general, the nomenclature used in this application is based on  
 5 *AutoNom*, a Beilstein Institute computerized system for the generation of IUPAC systematic nomenclature.

For example, a compound of Formula (I)



wherein R<sup>1</sup> is naphthyl, X is piperazinyl, and Y is -CO-R<sup>4</sup>, wherein R<sup>4</sup> is furanyl, is  
 10 named:

4-[4-(Furan-2-carbonyl)-piperazin-1-ylmethylene]-2-naphthalen-1-yl-4H-oxazol-5-one.

Similarly, a compound of Formula (I) wherein R<sup>1</sup> is benzofuranyl, X is piperazinyl, and Y is -R<sup>3</sup>, wherein R<sup>3</sup> is benzimidazolyl, is named:

15 2-Benzofuran-4-yl-4-[4-(1H-benzimidazol-2-yl)-piperazin-1-ylmethylene]-4H-oxazol-5-one.

Additionally, a compound of Formula (I) wherein R<sup>1</sup> is naphthyl, X is piperazinyl, and Y is -CO-NH-R<sup>5</sup>, wherein R<sup>5</sup> is 3-fluorophenyl, is named:

20 4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid (3-fluoro-phenyl)-amide.

Similarly, a compound of Formula (I) wherein R<sup>1</sup> is benzofuranyl, X is piperazinyl, and Y is -C(NH)-NH-R<sup>7</sup>, wherein R<sup>7</sup> is pyridyl, is named:

4-(2-Benzofuran-7-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-piperazine-1-carboxamidine.

### Preferred Compounds

Among the compounds of the present invention set forth in the Summary of the Invention, certain additional compounds are preferred. For example, preferred compounds of Formula (I), or individual isomers, racemic or non-  
5 racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof, include:

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid phenylamide (**208**, Example 13);

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-  
10 piperazine-1-carboxamidine (**276**, Example 16);

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamidine (**334**, Example 19);

4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-naphthalen-1-yl-4H-oxazol-5-one (**416**, Example 24);

15 4-[2-(4-Fluoro-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide (**212**, Example 13);

4-[2-(4-Fluoro-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamidine (**278**, Example 16);

4-[2-(4-Fluoro-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-  
20 piperazine-1-carboxamidine (**336**, Example 19);

4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(4-fluoro-naphthalen-1-yl)-4H-oxazol-5-one (**418**, Example 24);

4-[4-(4,5-Dihydro-1H-imidazol-2-yl)-piperazin-1-ylmethylene]-2-(4-fluoro-naphthalen-1-yl)-4H-oxazol-5-one (**500**, Example 30);

25 4-[2-(7-Fluoro-benzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide (**248**, Example 14);

4-[2-(7-Fluoro-benzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamidine (as hydrochloride **324**, Example 17);

4-[2-(7-Fluoro-benzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-  
30 piperazine-1-carboxamidine (as hydrochloride **382**, Example 20);

4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(7-fluoro-benzofuran-4-yl)-4H-oxazol-5-one (**464**, Example 25);

4-(2-Benzofuran-4-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid phenylamide (**250**, Example 14);

4-(2-Benzofuran-4-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-piperazine-1-carboxamidine (as hydrochloride **326**, Example 17);

5 4-(2-Benzofuran-4-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamidine (as hydrochloride **338**, Example 20);

2-Benzofuran-4-yl-4-[4-(1H-benzoimidazol-2-yl)-piperazin-1-ylmethylene]-4H-oxazol-5-one (as hydrochloride **458**, Example 25);

4-[2-(2,3-Dihydro-benzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide (**254**, Example 14);

4-[2-(2,3-Dihydro-benzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamidine (as hydrochloride **330**, Example 17);

4-[2-(2,3-Dihydro-benzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-piperazine-1-carboxamidine (as hydrochloride **386**, Example 20);

15 4-(2-Benzofuran-7-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid phenylamide (**252**, Example 14);

4-(2-Benzofuran-7-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-piperazine-1-carboxamidine (as hydrochloride **318**, Example 17);

4-(2-Benzofuran-7-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamidine (as hydrochloride **332**, Example 20);

2-Benzofuran-7-yl-4-[4-(4,5-dihydro-1H-imidazol-2-yl)-piperazin-1-ylmethylene]-4H-oxazol-5-one (as hydrochloride **498**, Example 30);

4-[2-(2,3-Dihydro-benzofuran-7-yl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide (**242**, Example 14);

25 4-[2-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamidine (**256**, Example 14);

4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-4H-oxazol-5-one (**466**, Example 25); and

2-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-4-[4-(4,5-dihydro-1H-imidazol-2-yl)-piperazin-1-ylmethylene]-4H-oxazol-5-one (**504**, Example 30).

More preferred compounds of Formula (I), or individual isomers, racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof, include:

- 4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid phenylamide (**208**, Example 13);
- 4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-piperazine-1-carboxamidine (**276**, Example 16);
- 4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamidine (**334**, Example 19);
- 4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-naphthalen-1-yl-4H-oxazol-5-one (**416**, Example 24);
- 4-[2-(4-Fluoro-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide (**212**, Example 13);
- 4-[2-(4-Fluoro-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamidine (**278**, Example 16);
- 4-[2-(4-Fluoro-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-piperazine-1-carboxamidine (**336**, Example 19);
- 4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(4-fluoro-naphthalen-1-yl)-4H-oxazol-5-one (**418**, Example 24);
- 4-[2-(7-Fluoro-benzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide (**248**, Example 14);
- 4-[2-(7-Fluoro-benzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamidine (as hydrochloride **324**, Example 17);
- 4-[2-(7-Fluoro-benzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-piperazine-1-carboxamidine (as hydrochloride **382**, Example 20);
- 4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(7-fluoro-benzofuran-4-yl)-4H-oxazol-5-one (**464**, Example 25);
- 4-(2-Benzofuran-4-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid phenylamide (**250**, Example 14);
- 4-(2-Benzofuran-4-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-piperazine-1-carboxamidine (as hydrochloride **326**, Example 17);

4-(2-Benzofuran-4-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamide (as hydrochloride **338**, Example 20); and

2-Benzofuran-4-yl-4-[4-(1H-benzoimidazol-2-yl)-piperazin-1-ylmethylene]-4H-oxazol-5-one (as hydrochloride **458**, Example 25).

5 Even more preferred compounds of Formula (I), wherein the compound is present as an individual isomer, a racemic or non-racemic mixture of isomers, or a pharmaceutically acceptable salt or solvate thereof, include:

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-piperazine-1-carboxamide (**276**, Example 16);

10 4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamide (**334**, Example 19);

4-[2-(4-Fluoro-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamide (**278**, Example 16);

15 4-[2-(4-Fluoro-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-piperazine-1-carboxamide (**336**, Example 19);

4-(2-Benzofuran-4-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-piperazine-1-carboxamide (as hydrochloride **326**, Example 17); and

4-(2-Benzofuran-4-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamide (as hydrochloride **338**, Example 20).

20 Another preferred group includes the pharmaceutically acceptable salts or solvates of the compounds of the present invention wherein the pharmaceutically acceptable salts are formed from acetic acid, hydrochloric acid, sulphuric acid, methanesulfonic acid, maleic acid, phosphoric acid, tartaric acid, citric acid, sodium, potassium, calcium, zinc, and magnesium.

25

### GENERAL SYNTHETIC SCHEME

Compounds of this invention can be made by the methods depicted in the reaction schemes shown below.

30 The starting materials and reagents used in preparing these compounds are either available from commercial suppliers, such as Aldrich Chemical Co., or are prepared by methods known to those skilled in the art following procedures set forth in references such as *Fieser and Fieser's Reagents for Organic*

*Synthesis*, Wiley & Sons, New York, 1991, Volumes 1-15; *Rodd's Chemistry of Carbon Compounds*, Elsevier Science Publishers, 1989, Volumes 1-5 and Supplementals; and *Organic Reactions*, Wiley & Sons, New York, 1991, Volumes 1-40. These schemes are merely illustrative of some methods by which  
5 the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not  
10 limited to, filtration, distillation, crystallization, chromatography, and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

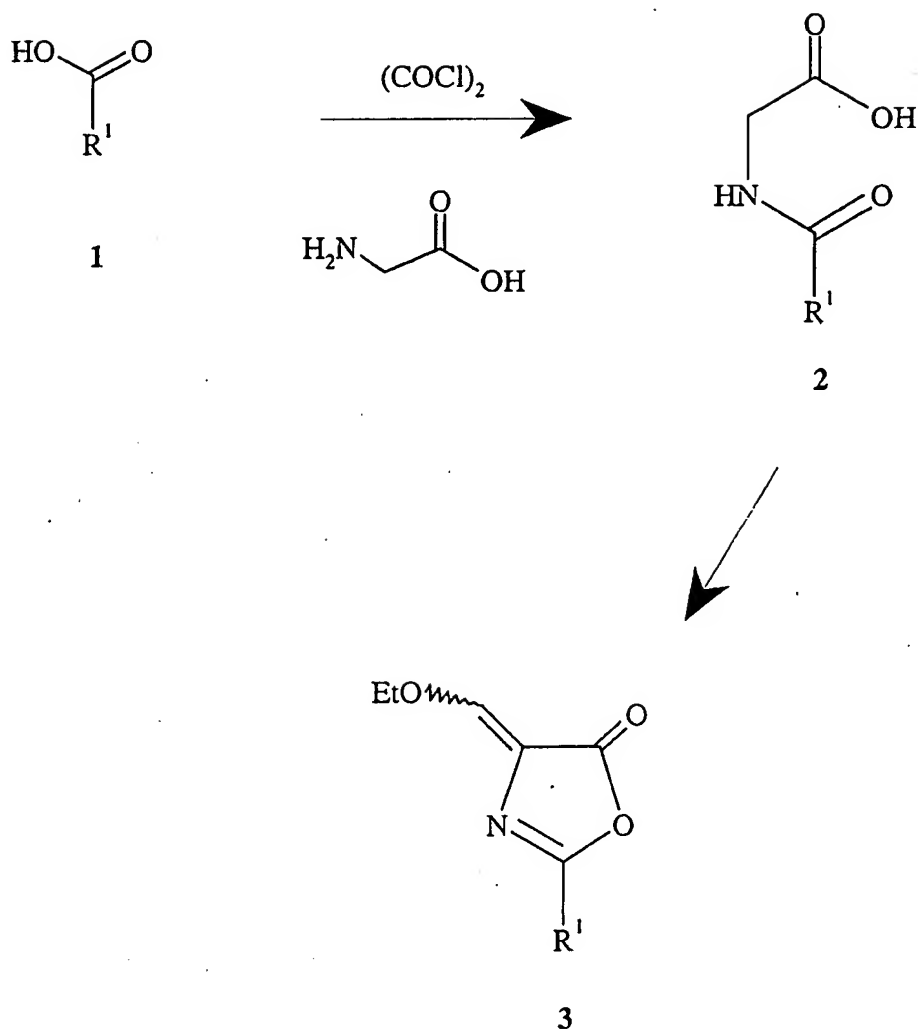
Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about -78°C to about  
15 150°C, more preferably from about 0°C to about 125°C.

Compounds of Formula (I) are prepared using general methods described in the literature. Particularly, intermediate compounds of structure **3** in which R<sup>1</sup> is as described herein can be prepared as described in, for example, Cornforth, J.W., *The Chemistry of Penicillin*, Princeton University Press, Princeton New  
20 Jersey, 1949, Chapter 21; Bland J.M. *et al.*, *Journal of Organic Chemistry*, 1984, 49, 1634-1636 and Kocevar M. *et al.*, *Liebigs Ann. Chem.*, 1990, 5, 501-503.

Generally, as set forth in reaction Scheme 1, a carboxylic acid **1** is first converted to the corresponding acid chloride, by treatment with, for example, oxalyl chloride, followed by conversion to the corresponding glycine amide **2**.  
25 The resulting acid-amide **2** can be cyclized using, for example, triethyl orthoformate and acetic anhydride at 80°C to yield the R<sup>1</sup>-substituted 4-ethoxymethylene-5-oxazolones **3**.

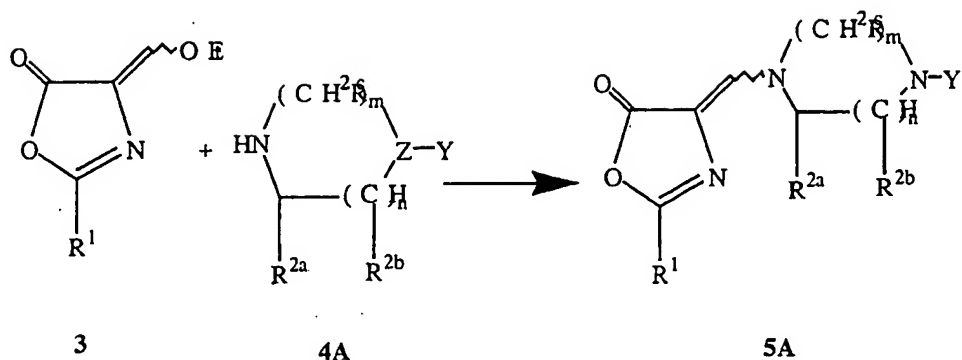


## SCHEME 1

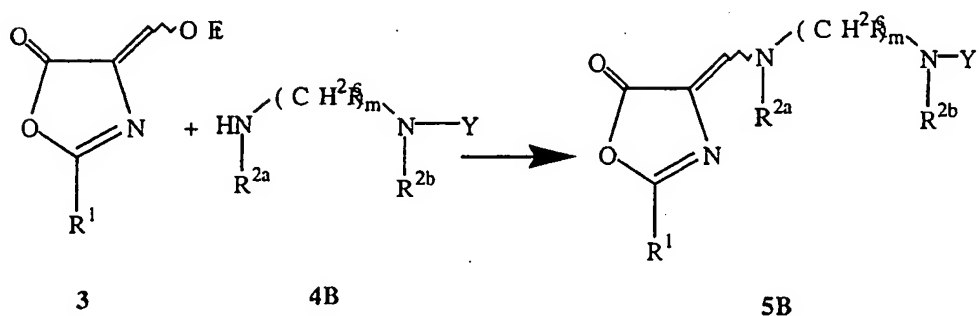


In general, the compounds of the present invention can be prepared by first alkylating an optionally substituted amine, such as 4A, 4B or 4C (wherein Y is as described above; see reaction Scheme 2) with an  $R^1$ -substituted 4-ethoxy-methylene-5-oxazolone 3 (prepared as set forth in reaction Scheme 1), to yield compounds 5A, 5B or 5C, respectively.

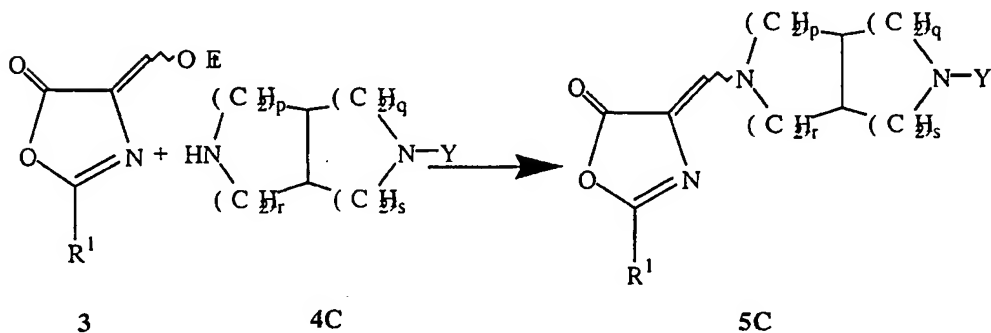
## SCHEME 2A



## SCHEME 2B



## SCHEME 2C



An alternative method of preparing the compounds of this invention is alkylation of a suitably mono-protected diamine, such as **6A**, **6B** or **6C**, with an  $R^1$ -substituted 4-ethoxymethylene-5-oxazolone **3** (prepared as set forth in reaction Scheme 1), to yield compounds **7A**, **7B** or **7C** (wherein P denotes a suitable protecting group as described herein, such as benzyl, benzyloxycarbonyl

(carbobenzyloxy; CBZ), p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, *tert*-butoxycarbonyl (BOC), trifluoroacetyl, preferably BOC or CBZ), and then deprotecting (see reaction Scheme 3), to yield compounds **8A**, **8B** or **8C**.

Compounds **5A**, **5B** and **5C** can be then prepared by adding an appropriately activated Y, wherein Y is as defined herein, onto compounds **8A**, **8B** or **8C**, respectively.

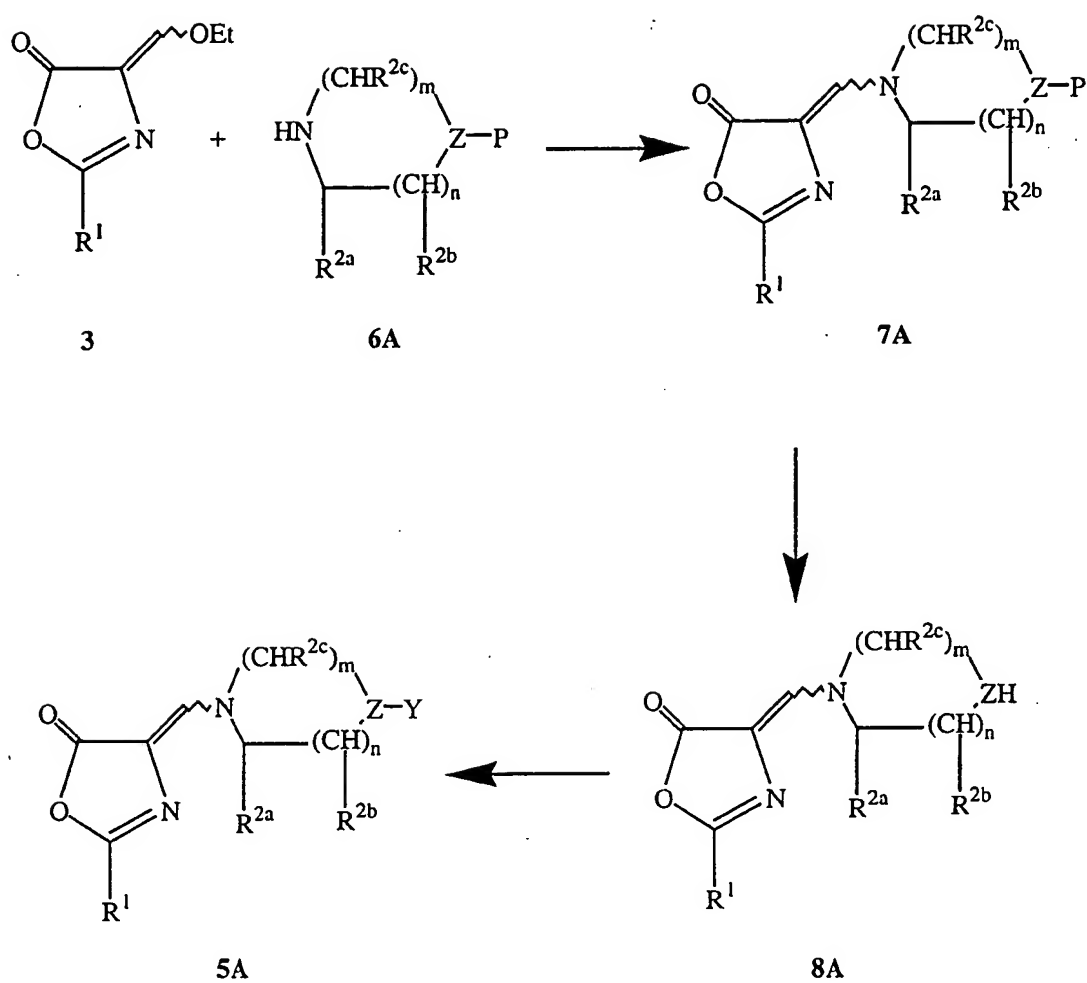
The alkylation of compounds **6A**, **6B** or **6C** can be carried out neat at about 0° to about 250° C, typically at about 10° to about 150° C and preferably at about 20° to about 100° C, requiring about 1 to about 24 hours (for further details see, e.g., Example 2, *infra*). Alternatively, the reaction can be carried out in a suitable inert organic solvent (e.g., acetonitrile, methyl sulfoxide (DMSO), N,N-dimethylformamide (DMF), N-methylpyrrolidone (NMP), benzene, toluene, any appropriate mixture of suitable solvents, etc., preferably acetonitrile or DMSO) with a suitable base present (e.g., sodium carbonate, potassium carbonate, cesium carbonate, 2,4,6-trimethylpyridine, triethylamine, N,N-diisopropylethylamine, etc., preferably sodium carbonate, triethylamine, or N,N-diisopropylethylamine) at 0° to about 250° C, typically at about 10° to about 150° C and preferably at about 20° to about 100° C, and preferably at reflux, requiring about 2 to about 72 hours (for further details see, e.g., Example 3, *infra*).

Deprotection of compounds **7A**, **7B** or **7C**, in which a nitrogen protective group is present, can be effected by any means which remove the protective group and give the desired product **8A**, **8B** or **8C**. As described herein, a detailed description of the techniques applicable to protective groups and their removal can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, Wiley and Sons, New York, 1991. For example, a convenient method of deprotection when the protective group is N-*tert*-butoxycarbonyl can be carried out with trifluoroacetic acid or hydrochloric acid in a suitable inert organic (e.g., ethyl acetate, dichloromethane, tetrahydrofuran (THF), hexamethylphosphoramide (HMPA), or any appropriate mixture of suitable solvents, etc., preferably THF or ethyl acetate) at 0° to about 250° C, typically at about 10° to about 150° C and preferably at about 20° to about 100° C, and requires about 8 to about 24 hours (for further details see, e.g., Example 3, *infra*).

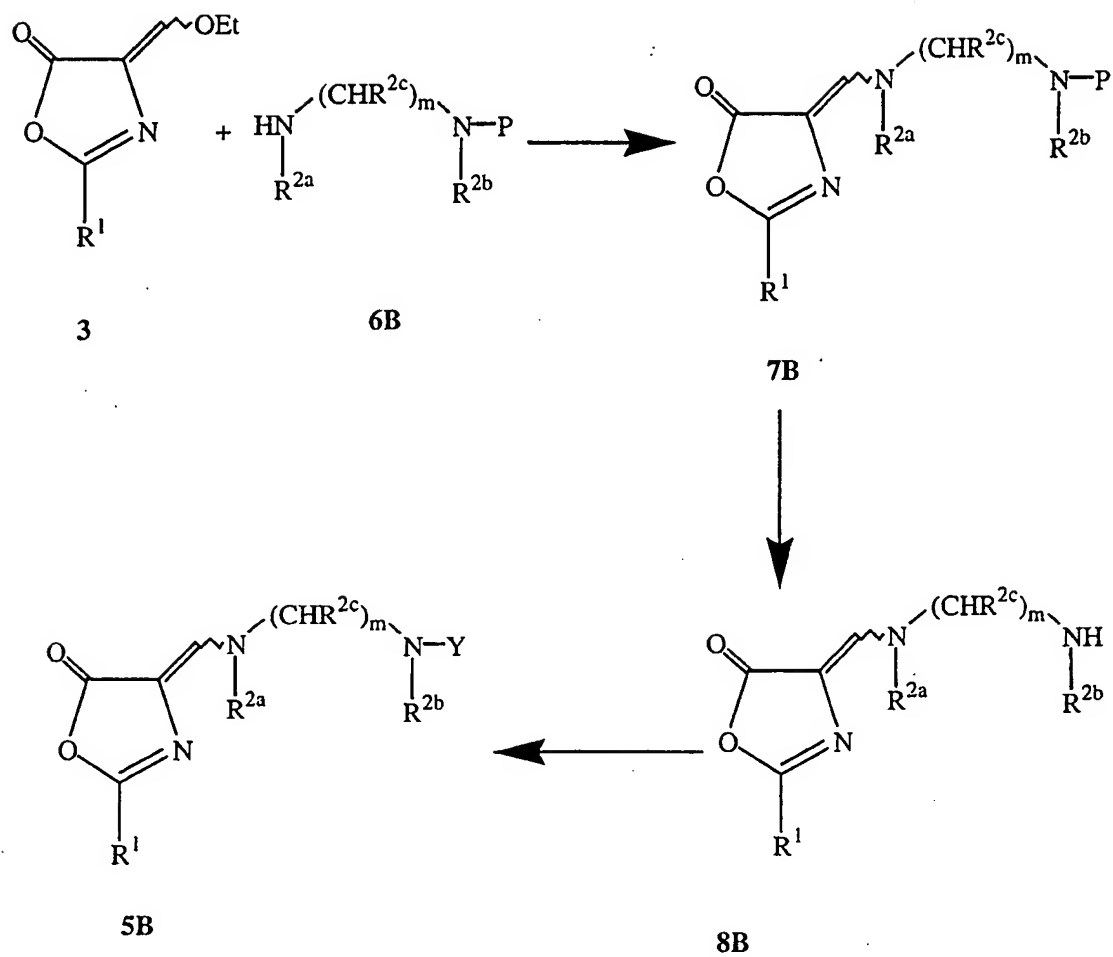
Deprotection, when the protective group is benzyl or CBZ, can be carried out by catalytic hydrogenation. The hydrogenation is carried out with a suitable catalyst (e.g., 10% palladium on carbon (10% Pd/C), palladium hydroxide, palladium acetate, etc. preferably 10% Pd/C) in the presence of ammonium formate and in  
5 an appropriate solvent, typically an alcohol (e.g., ethanol, methanol, isopropanol, any appropriate mixture of alcohols, etc.), preferably methanol, at about 0° to about 250° C, typically at about 10° to about 150° C and preferably at about 20° to about 100° C and preferably at reflux. Alternatively, the benzyl group can be removed by treating the protected compound with the catalyst under a hydrogen  
10 atmosphere at 0 to 50 psi, typically at 10 to 20 psi and preferably at approximately 15 psi, at about 0° to about 250° C, typically at about 10° to about 150° C, and preferably at about 20° to about 100° C.

Compounds **5A**, **5B** and **5C** can then prepared by adding an appropriately activated Y, wherein Y is as defined herein, onto compounds **8A**, **8B** or **8C**,  
15 respectively. The substitution reaction is carried out at about 0° to about 250° C, typically at about 10° to about 150° C and preferably at about 20° to about 100° C, requiring about 1 to about 24 hours. The reaction can be carried out in a suitable inert organic solvent (e.g., acetonitrile, methyl sulfoxide (DMSO), N,N-dimethylformamide (DMF), N-methylpyrrolidione (NMP), benzene, toluene,  
20 any appropriate mixture of suitable solvents, etc., preferably acetonitrile or DMSO) with a suitable base optionally present, e.g., sodium carbonate, potassium carbonate, cesium carbonate, 2,4,6-trimethylpyridine, triethylamine, N,N-diisopropylethylamine (Hünig's base), etc., preferably sodium carbonate, triethylamine, N,N-diisopropylethylamine (Hünig's base); for further details see,  
25 e.g., Examples 4, 5, 6 and 7, *infra* at about 0° to about 250° C, typically at about 10° to about 150° C and preferably at about 20° to about 100° C and more preferably at reflux, requiring 2 to 72 hours, *see, e.g., Example 5, infra*.

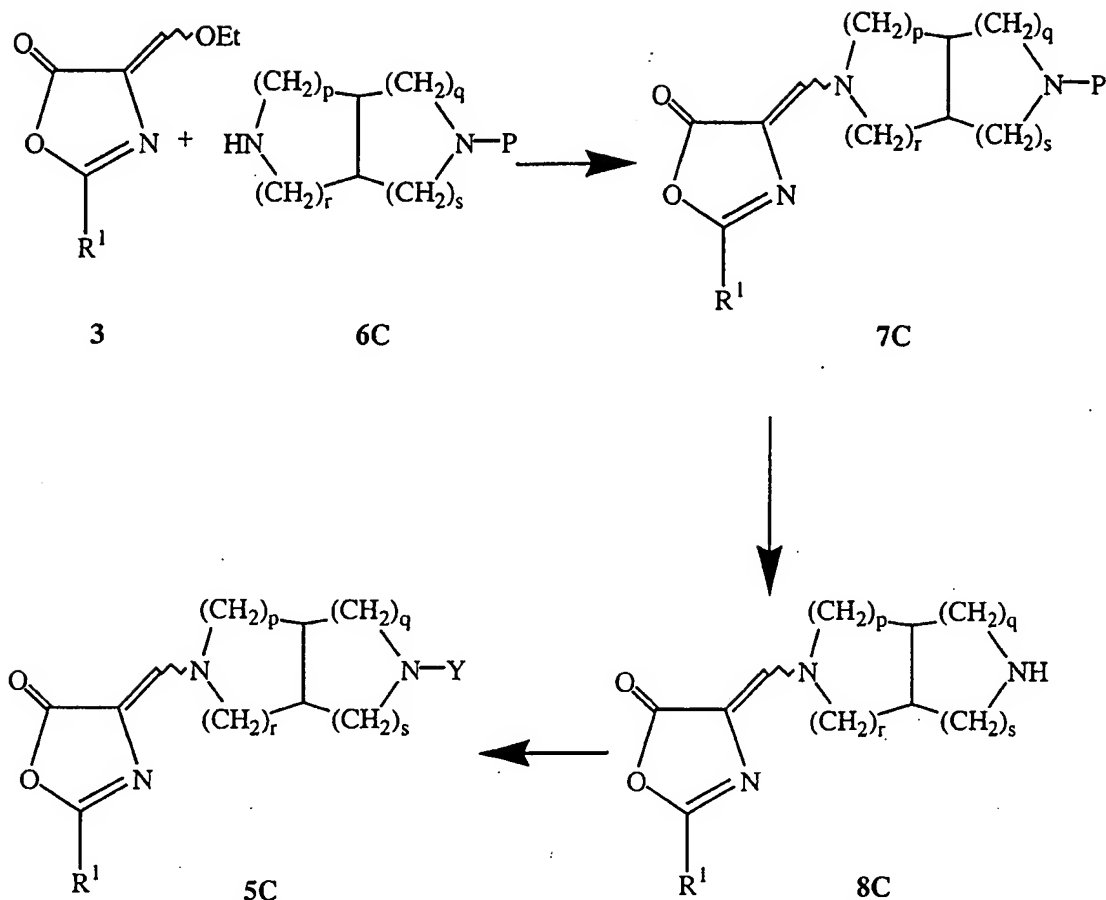
## SCHEME 3A



## SCHEME 3B



## SCHEME 3C

Administration and Pharmaceutical Compositions

The invention provides pharmaceutical compositions comprising a  
 5 compound of the present invention or a pharmaceutically acceptable salt, solvate  
 or derivative thereof together with one or more pharmaceutically acceptable  
 carriers, and optionally other therapeutic and/or prophylactic ingredients.

In general, the compounds of this invention will be administered in a  
 therapeutically effective amount by any of the accepted modes of administration  
 10 for agents that serve similar utilities. Suitable dosage ranges are about 1 mg to  
 about 500 mg daily, preferably about 1 mg to about 100 mg daily, and more  
 preferably about 1 mg to about 30 mg daily, depending upon numerous factors  
 such as the severity of the disease state to be treated, the age and relative

health of the subject, the potency of the compound used, the route and form of administration, the indication towards which the administration is directed, and the preferences and experience of the medical or veterinary practitioner involved. One of ordinary skill in the art of treating such a disease state will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of the compounds of this invention for use in treating a given disease state.

In general, compounds of this invention will be administered as pharmaceutical formulations including those suitable for oral (including buccal and sub-lingual), rectal, nasal, topical, pulmonary, vaginal or parenteral (including intramuscular, intraarterial, intrathecal, subcutaneous, and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The preferred manner of administration is oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. The pharmaceutical composition may be employed as solids, such as tablets or filled capsules, semisolids, powders, sustained release formulations, or liquids such as solutions, suspensions, emulsions, elixirs, or filled capsules for oral use; or in the form of suppositories for rectal or vaginal administration; or in the form of sterile injectable solutions for parenteral use. Formulations containing about 0.01 to 100 milligrams, preferably 1 to 50 milligrams, more preferably 1 to 10 milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of the present invention may be formulated in a wide variety of oral administration dosage forms. The pharmaceutical compositions and dosage forms may comprise the compounds of the invention or its pharmaceutically acceptable salt or solvate as the active component. The



pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from one to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be as solid forms suitable for oral administration.

Other forms suitable for oral administration include liquid form preparations such as emulsions, syrups, elixirs, aqueous solutions, aqueous suspensions, or solid form preparations which are intended to be converted shortly before use to liquid form preparations. Emulsions may be prepared in solutions in aqueous propylene glycol solutions or may contain emulsifying agents such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents. Solid form preparations include solutions, suspensions, and emulsions, and may contain, in addition to the active component, colorants, flavors, stabilizers,

buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The compounds of the present invention may be formulated for parenteral administration (e.g., by injection, for example bolus injection or continuous  
5 infusion) and may be presented in unit dose form in ampules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, for example solutions in aqueous polyethylene glycol. Examples of oily or nonaqueous carriers, diluents, solvents or vehicles include  
10 propylene glycol, polyethylene glycol, vegetable oils (e.g., olive oil), and injectable organic esters (e.g., ethyl oleate), and may contain formulatory agents such as preserving, wetting, emulsifying or suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution for  
15 constitution before use with a suitable vehicle, e.g., sterile, pyrogen-free water.

The compounds of the present invention may be formulated for topical administration to the epidermis as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling  
20 agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. Formulations suitable for topical administration in the mouth include lozenges comprising active agents in a flavored base, usually sucrose and acacia or  
25 tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

The compounds of the present invention may be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty  
30 acid glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, for example, by stirring. The molten homogeneous

mixture is then poured into conveniently sized molds, allowed to cool, and to solidify.

The compounds of the present invention may be formulated for vaginal administration. Pessaries, tampons, creams, gels, pastes, foams or sprays, may  
5 contain agents in addition to the active ingredient, such carriers, known in the art to be appropriate.

The compounds of the present invention may be formulated for nasal administration. The solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The  
10 formulations may be provided in a single or multidose form. In the case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump.

15 The compounds of the present invention may be formulated for aerosol administration, particularly to the respiratory tract including intranasal administration. The compound will generally have a small particle size for example of the order of about 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. The active  
20 ingredient is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by a metered valve. Alternatively,  
25 the active ingredients may be provided in a form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethylcellulose and polyvinylpyrrolidone (PVP). The powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or  
30 cartridges of, e.g., gelatin or blister packs from which the powder may be administered by means of an inhaler.

When desired, formulations can be prepared with enteric coatings adapted for sustained or controlled release administration of the active ingredient.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Other suitable pharmaceutical carriers and their formulations are described in *Remington: The Science and Practice of Pharmacy* 1995, edited by E. W. Martin, Mack Publishing Company, 19th edition, Easton, Pennsylvania. Representative pharmaceutical formulations containing a compound of the present invention are described in Example 49.

In addition to being administered alone, an  $\alpha_{1B}$ -adrenergic receptors adrenergic receptor antagonist can be administered for the treatment of pain in combination with other appropriate compounds, such as, analgesics or anticonvulsants. Such compounds include, but are not limited to the following: agents used in the treatment of neuropathic pain including, but not limited to, tricyclic antidepressants (e.g., amitriptyline, imipramine, desipramine), anti-convulsants (e.g., gabapentin, carbamazepine, phenytoin) and local anesthetics (e.g., mexiletine, lidocaine); and agents used in the treatment of inflammatory pain including, but not limited to, NSAIDs (e.g., ibuprofen, naprosyn sodium, aspirin, diclofenac sodium, indomethacin, toletin), steroids (e.g., methylprednisone, prednisone), analgesics (e.g., acetaminophen), and opiates (e.g., tramadol, demerol, darvon, vicodin, fentanyl).

In view of the guidance provided herein concerning the present invention, other compounds, including other  $\alpha$ -adrenergic receptor ligands, that block  $\alpha_{1B}$ -adrenergic receptors can be examined by the teachings of the present specification to determine their usefulness in the treatment of pain. Determination of a compound's ability to selectively block  $\alpha_{1B}$ -adrenergic receptors can be performed as described in

Example 1. The usefulness of the compound for the treatment of pain can be evaluated as described herein in Examples 45-49. Binding assays, the evaluation of analgesic activity of a test compound, and/or the evaluation of other functional  $\alpha_1$ -adrenergic receptor-mediated activity of a test compound, as described herein, can be carried out concurrently and/or consecutively, in any order, and near or remote in time.

As stated above, the role of  $\alpha_{1B}$ -adrenergic receptor antagonists in analgesia has not been previously described. Experiments performed in support of the present invention suggest that  $\alpha_{1B}$ -adrenergic receptor antagonists may be useful in the treatment of acute, inflammatory, and neuropathic pain in a subject.

#### Pharmacology and Utility

Alpha<sub>1</sub>-adrenoceptors mediate the contractile state of smooth muscle tissue and are present in the human prostate, bladder neck and urethra. Sympathetic activity produces contraction of vascular smooth muscle which leads to elevated blood pressures. Alpha<sub>1</sub>-adrenoceptor stimulation also produces glycogenolysis, growth and hypertrophy of cardiac myocytes, and contraction of urethral and bladder neck smooth muscle, leading to increased resistance in urinary outflow. Thus, alpha<sub>1</sub>-adrenoceptor antagonists may be useful in preventing hypertension and treating disorders or symptoms related to uropathies, such as obstruction due to benign prostatic hyperplasia (BPH). (See U.S. Patent No. 5,859,014; Lepor, H., *The Prostate Supplement*, 1990, 3:75-84 and International Patent Publication No. WO 95/25726.)

Some drugs effective in the treatment of benign prostatic hyperplasia block alpha<sub>1A</sub>-adrenergic mediated contractions of the prostate. Alpha<sub>1A</sub>-adrenoceptors may mediate smooth muscle hyperplasia in the prostate, therefore a selective alpha<sub>1A</sub>-adrenoceptor antagonist may have utility not only in mitigating the excessive prostatic constriction, but also in preventing progression of tissue hyperplasia.

Experimental evidence supports a therapeutic role for alpha<sub>1</sub>-adrenoceptor antagonists in treating prostatic hyperplasia. (See for example,

Lepor, H., *The Prostate Supplement*, 1990, 3, 75-84.) Obstruction of the urinary tract can occur as a result of prostatic hyperplasia and excessive prostatic constriction of the urethra. This in turn leads to diminished urinary flow rates and an increased urgency and frequency of urination.

5 In a preferred embodiment, the compounds of this invention are useful for treating disease states which can be ameliorated by modulation, preferably by blockade of  $\alpha_1$ -adrenoceptors, such as reduction or alleviation of urinary tract disorders, for example, pelvic hypersensitivity (including interstitial cystitis, prostatitis, pelvic pain syndrome, infectious cystitis, prostatodynia, and the like),  
10 overactive bladder, urinary frequency, nocturia, urinary urgency, detrusor hyperreflexia, outlet obstruction, prostatitis, urge incontinence, urethritis, idiopathic bladder hypersensitivity, and the like. Compounds of this invention may also be useful for treating male erectile dysfunction and female sexual dysfunction.

15 In a more preferred embodiment, the compounds of the invention are useful for treating disease states which can be ameliorated by blockade of  $\alpha_{1B}$ -adrenoceptors.  $\alpha_{1B}$ -adrenoceptors are present in the liver, heart and cerebral cortex and are believed to be involved in mediating vascular contractile and blood pressure responses. Additionally,  $\alpha_{1B}$ -adrenoceptors  
20 are also present in areas of the spinal cord which receive input from sympathetic neurons originating in the pontine micturition center and are presumed to be involved in the regulation of bladder function. Selective blockade of the  $\alpha_{1B}$ -adrenoceptor may lead to the symptomatic treatment of pelvic hypersensitivity including interstitial cystitis, prostatitis, pelvic pain syndrome, infectious cystitis, prostatodynia, and the like, and symptoms associated with overactive bladder.  
25

Several clinical observations suggest a therapeutic role for the  $\alpha_{1B}$ -adrenoceptor antagonists in the prevention of disease states of the urinary tract, such as pelvic hypersensitivity (including interstitial cystitis, prostatitis, pelvic pain syndrome, infectious cystitis, prostatodynia, and the like), urethritis, overactive  
30 bladder (manifested as urge incontinence), detrusor hyperreflexia, outlet

obstruction (resulting from benign prostatic hypertrophy and prostatitis), and other conditions of idiopathic bladder hypersensitivity.

Additionally, the  $\alpha_{1B}$ -adrenoceptor antagonists are useful as analgesic/ antihyperalgesic therapies for treating pain, including symptoms of acute pain, inflammatory pain, neuropathic pain (including thermal and mechanical hyperalgesia as well as thermal and mechanical allodynia), complex regional pain syndromes (including reflex sympathetic dystrophy, causalgia and sympathetically maintained pain).

10        Assays:

The pharmacology of the compounds of this invention was determined by art-recognized procedures. *In vitro* techniques for determining the affinities of test compounds in radioligand binding and functional assays are described in Example 45.

15        The effect of the compounds of this invention on blood pressure can be evaluated by any method known in the art. Examples of such methods are as follows.

Rat *In Vivo*, Blood Pressure Assay: An *in vivo* assay for measuring the blood pressure lowering effects of test compounds in normotensive rats is described in Example 46.

Rat *In Vivo*, Tilt-Response Assay: The following describes an *in vivo* assay in normotensive rats for measuring the propensity of a test compound to inhibit the reflex maintenance of basal blood pressure levels in response to vertical tilt.

25        Normotensive rats (0.25 to 0.45 kg) are fasted for 18 hours and anesthetized with ether. The right femoral vein is isolated and cannulated with a fluid-filled polyethylene cannulae for bolus administration of test substances. The right femoral artery is isolated and cannulated with a fluid-filled polyethylene cannula connected to an external pressure transducer for monitoring mean  
30        arterial blood pressure (MAP).

The rats are restrained in a supine position and allowed to recover from anesthesia. Following a 30- minute period for stabilization, test compound or vehicle are administered, *i.v.*, and blood pressure is monitored continuously while the rats are tilted vertically at 30 to 60 degrees from supine at 15, 30 and 45 minutes post-administration.

Dog *In Vivo*, Blood and Intraurethral Pressure Assay: The following describes an *in vivo* assay for measuring the relative effect of a test compound on hypogastric nerve stimulation-induced increases in intraurethral pressure and phenylephrine-induced increases in diastolic blood pressure in anesthetized dog.

Mongrel dogs (10 to 20 kg) are fasted for 12 to 18 hours and anesthetized with phenobarbital sodium (35 mg/kg, *i.v.*). An endotracheal tube is inserted and thereafter the lungs are mechanically ventilated with room air. The right femoral vein is isolated and cannulated with two polyethylene cannulae, one for the administration of a continuous infusion of phenobarbital sodium (5 to 10 mg/kg/hr) and the other for bolus administration of test substances. The right femoral artery is isolated and cannulated to the abdominal aorta with a fluid filled polyethylene cannula connected to an external pressure transducer for monitoring diastolic aortic pressure (DAP). The bladder is exposed via a ventral midline abdominal incision and emptied of urine through a 22-gauge needle. The bladder is cannulated through a stab incision with a water-filled balloon catheter connected to an external pressure transducer for monitoring prostatic intraurethral pressure (IUP). The right hypogastric nerve (HGN) is carefully isolated and attached to a Dastre's electrode for nerve stimulation.

The preparation is allowed to stabilize for a least 30 minutes and must have a stable basal IUP for not less than 15 minutes prior to commencement of the assay protocol. The HGN is stimulated (20-50 V, 10 Hz, 10 msec pulse train for 10 sec) to induce a measurable increase in IUP and then phenylephrine (PE) is administered by bolus injection (0.5 to 0.6 µg/kg, *i.v.*) to induce a measurable increase in DAP. The HGN stimulation and PE bolus injection are repeated every 5 minutes until three consecutive reproducible increases in IUP and DAP are achieved. Vehicle (0.1 to 0.3 mL/kg) is administered and 20 minutes later the HGN stimulation and PE bolus injection are repeated. Test compound is



then administered and 20 minutes later the HGN stimulation and PE bolus injection are repeated. Test compound is administered approximately every 20 minutes, increasing the dose until maximal or near maximal inhibition of the increases in IUP and DAP is attained.

5       The analgesic activity of the compounds of this invention can be evaluated by any method known in the art. Examples of such methods are as follows.

Tail Flick Model: The tail-flick test (D'Amour et al. (1941) *J. Pharmacol. Exp. and Ther.* 72:74-79) is a model of acute pain. A towel-wrapped rat is placed on a test stage such that a focused light source beams on the dorsal surface of the rat's tail. A photosensor is present on the test stage located opposite the  
10       light source and below the rat's tail. To begin the test the rat's tail blocks the light, thus preventing the light reaching the photosensor. Latency measurement begins with the activation of the light source. When a rat moves or flicks its tail the photosensor detects the light source and stops the measurement. The test  
15       measures the period of time (duration) that the rat's tail remains immobile (latent). Rats are tested pre-dose and then tested at various times post-dose. The light source is set to an intensity that produced a tail response latency of about 3 seconds when applied to the tails of pre-dose rats (rats to which no compounds have been administered).

20       Rat Tail Immersion Model: The rat tail immersion assay is also a model of acute pain. A rat is loosely held in hand while covered with a small folded thin cotton towel with its tail exposed. The tip of the tail is dipped into a, e.g., 52 °C water bath to a depth of two inches. The rat responds by either wiggling of the tail or withdrawal of the tail from the water; either response is scored as the  
25       behavioral end-point. A rat is tested for a pre-dose tail response latency (TRL) score. It is then dosed with a selected agent and, following dosing, retested for tail response latency at various times post-dosing.

Carrageenan-induced Paw Hyperalgesia Model: The carrageenan paw hyperalgesia test is a model of inflammatory pain. A subcutaneous injection of  
30       carrageenan is made into the left hindpaws of rats. The mammals are dosed with a selected agent before, e.g., 30 minutes, the carrageenan injection or after, e.g., two hours, the carrageenan injection. Paw pressure sensitivity for each

animal is tested with an analgesymeter three hours after the carrageenan injection. See, Randall et al., *Arch. Int. Pharmacodyn.*, 1957, 111:409-419.

The effects of selected agents on carrageenan-induced paw edema can also be examined. This test (see, Vinegar et al., *J. Pharmacol. Exp. Ther.*, 1969, 5 166:96-103) allows an assessment of the ability of a compound to reverse or prevent the formation of edema evoked by paw carrageenan injection. The paw edema test is carried out using a plethysmometer for paw measurements. After administration of a drug, a carrageenan solution is injected subcutaneously into the lateral foot pad on the plantar surface of the left hind paw. At three hours 10 post-carrageenan treatment, the volume of the treated paw (left) and the untreated paw (right) is measured using a plethysmometer.

Formalin Behavioral Response Model: The formalin test is a model of acute, persistent pain. Response to formalin treatment is biphasic (Dubuisson et al., *Pain*, 1977, 4:161-174). The Phase 1 response is indicative of a pure 15 nociceptive response to the irritant. Phase 2, typically beginning 20 to 60 minutes following injection of formalin, is thought to reflect increased sensitization of the spinal cord.

Von Frey Filament Test: The effect of  $\alpha_{1B}$ -adrenergic receptor antagonists on mechanical allodynia can be determined by the von Frey filament 20 test in rats with a tight ligation of the L-5 spinal nerve: a model of painful peripheral neuropathy. The surgical procedure is performed as described by Kim et al., *Pain*, 1992, 50:355-363. A calibrated series of von Frey filaments are used to assess mechanical allodynia (Chaplan et al., *J. Neurosci. Methods*, 1994, 53:55-63). Filaments of increasing stiffness are applied perpendicular to the 25 midplantar surface in the sciatic nerve distribution of the left hindpaw. The filaments are slowly depressed until bending occurred and are then held for 4-6 seconds. The filament application order and number of trials were determined by the up-down method of Dixon (Chaplan et al., *supra*). Flinching and licking of the paw and paw withdrawal on the ligated side are considered positive responses.

30 Chronic Constriction Injury: Heat and cold allodynia responses can be evaluated as described below in rats having a chronic constriction injury (CCI). A

unilateral mononeuropathy is produced in rats using the chronic constriction injury model described in Bennett et al., *Pain*, 1988, 33:87-107.

CCI is produced in anesthetized rats as follows. The lateral aspect of each rat's hind limb is shaved and scrubbed with Nolvasan. Using aseptic techniques, an incision is made on the lateral aspect of the hind limb at the mid-thigh level. The biceps femoris is bluntly dissected to expose the sciatic nerve. On the right hind limb of each rat, four loosely tied ligatures (for example, Chromic gut 4.0; Ethicon, Johnson and Johnson, Somerville, NJ) are made around the sciatic nerve approximately 1-2 mm apart. On the left side of each rat, an identical dissection is performed except that the sciatic nerve is not ligated (sham). The muscle is closed with a continuous suture pattern with, e.g., 4-0 Vicryl (Johnson and Johnson, Somerville, NJ) and the overlying skin is closed with wound clips. The rats are ear-tagged for identification purposes and returned to animal housing.

Radiant Heat Model: An *in vivo* assay for measuring the pain response to radiant heat in neuropathic rats is described in Example 47. Generally, CCI rats are tested for thermal hyperalgesia at least 10 days post-op. The test apparatus consists of an elevated heated (26.7-27.8°C or 80-82°F) glass platform. Eight rats at a time, representing all testing groups, are confined individually in inverted plastic cages on the glass floor of the platform at least 15 minutes before testing. A radiant heat source placed underneath the glass is aimed at the plantar hind paw of each rat. The application of heat is continued until the paw is withdrawn (withdrawal latency) or the time elapsed is 20 seconds. This trial is also applied to the sham operated leg. Two to four trials are conducted on each paw, alternately, with at least 5 minutes interval between trials. The average of these values represents the withdrawal latency.

Cold Allodynia Model: The test apparatus and methods of behavioral testing is described in Ford et al., *Analgesia*, 1997, 3:111-118. An *in vivo* assay for measuring the pain response to cold allodynia model in neuropathic rats is described in Example 48.

The apparatus for testing cold allodynia in neuropathic (CCI) rats consists of a Plexiglass chamber with a metal plate 6 cm from the bottom of the chamber.

The chamber is filled with ice and water to a depth of 2.5 cm above the metal plate, with the temperature of the bath maintained at 0-4 °C throughout the test.

Each rat is placed into the chamber individually, a timer started, and the animal's response latency was measured to the nearest tenth of a second. A  
5 "response" is defined as a rapid withdrawal of the right ligated hindpaw completely out of the water what the animal is stationary and not pivoting. An exaggerated limp while the animal is walking and turning is not scored as a response. The animals' baseline scores for withdrawal of the ligated leg from the water typically range from 7-13 seconds. The maximum immersion time is 20  
10 seconds with a 20-minute interval between trials.

Motor Activity: The effects of  $\alpha_{1B}$ -adrenergic receptor antagonists on general locomotor activity and sedation can be examined. Locomotor deficits or sedation are both common side effects of potential analgesic compounds.

For the locomotor activity test (Winter, C.A., and L. Flataker, *J. Pharmacol.*  
15 *Exp. Therap.* **103**:93-105, 1951), rats are placed in individual plexiglass cages and allowed to move freely. The photobeam array (Photobeam Activity System, San Diego Instruments, San Diego, CA), comprises an infrared photobeam which is emitted by photodiodes on one side of the cage and detected by transistors on the opposite surface of the cage. The array is placed around the exterior of the cage.  
20 When an animal moves within the cage light beams are broken in succession. The infrared photobeam breaks can be recorded on a data file generated by the Photobeam Activity System software. The activity of each study animal is typically monitored every 15 seconds for 15 minutes.

Functional Activity: The functional  $\alpha_1$ -adrenergic receptor activity of a test  
25 compound can be determined by art-recognized procedures. Such studies are conducted to determine whether a test compound exhibits agonist or antagonist activity at  $\alpha_1$ -adrenergic receptor. Such activity can be indicative of potential side effects. Examples of *in vitro* and *in vivo* assays for measuring the relative effect of a test compound on  $\alpha_1$ -adrenergic receptor-mediated activity, either agonist or  
30 antagonist activity, are as follows.

$\alpha_1$ -Adrenergic Receptor *In Vitro* Assay in Tissue Isolated from Rabbit and

Rat: Thoracic aorta are isolated from rats and immediately immersed in Krebs' solution (comprising in mM concentrations: NaCl, 118.5; NaHCO<sub>3</sub>, 25; dextrose, 5; KCl, 4.8; CaCl<sub>2</sub>, 2.5; MgSO<sub>4</sub>, 1.2; KH<sub>2</sub>PO<sub>4</sub>, 1.2; cocaine, 0.03; corticosterone, 0.03; propranolol, 0.001; ascorbic acid, 0.1; and indomethacin, 0.01). The aortas are  
5 dissected free from extraneous tissue and then a cross-sectional ring approximately 3 mm in length is cut from the most proximal segment. The aortic rings are suspended vertically in 10 mL tissue baths and bathed in Krebs' solution maintained at 37°C and constantly aerated with a 95% O<sub>2</sub>:5% CO<sub>2</sub> gas mixture. A resting tension (preload) of 1 g is applied to each aortic ring and thereafter periodically readjusted to maintain a 1  
10 g resting tension throughout the duration of the assay.

Urinary bladders are emptied and isolated from rabbits. Bladders are dissected free from extraneous tissue and then a cross sectional ring of bladder neck tissue is cut above the urethra to approximately one third of the way up the bladder. The bladder neck is cut parallel to the longitudinal muscle fibers to give flat section of  
15 muscle tissue and then the flat section is cut parallel to the longitudinal muscle to give several flat strips. Strips of bladder tissue are suspended vertically in 10 mL tissue baths and bathed in Krebs' solution maintained at 33°C. and constantly aerated with a 95% O<sub>2</sub>:5% CO<sub>2</sub> gas mixture. A resting tension of 5 g was applied to each urinary bladder strip. The strips are allowed to relax to a resting tension of 1 g and thereafter  
20 periodically readjusted to maintain the 1 g resting tension throughout the duration of the assay.

The aortic ring or urinary bladder strip preparations are allowed to equilibrate for 60 minutes during which period the bath solution is replaced every 15 minutes. The tissue is then exposed to bath solution containing norepinephrine (0.1 to 10 µM)  
25 and once a steady state contraction is produced the tissue is exposed to bath solution free of norepinephrine, replacing the solution twice every 5 minutes for 30 minutes. The aortic rings are exposed to norepinephrine and the urinary bladder strips to phenylephrine in a cumulative concentration fashion. That is, the isolated tissue is exposed to bath solution containing a threshold concentration of either  
30 norepinephrine or phenylephrine until a steady state contractile response is attained and then the concentration of agonist is cumulatively increased by 0.5 log increments

until a maximal or near maximal response is attained.

The tissue is then exposed to solution free of agonist compound, replacing the solution twice every 5 minutes for 30 minutes. After baseline tension is established and readjusted to 1 g, the tissue is exposed to bath solution containing  
5 the test compound, replacing the solution every 15 minutes for 60 minutes. In the presence of the test compound, the tissue again is exposed to either norepinephrine or phenylephrine in a cumulative concentration fashion, increasing the agonist concentration until a maximal or near maximal response was achieved.

The concentration ratio (CR) of agonist necessary to produce equiactive  
10 responses in the absence and presence of the test compound is determined. Relying on the concentration ratio, the assay concentration (molar) of the test compound, and the relationship

$$pA_2 = -\log([test\ compound]/(CR-1))$$

the negative log of the dissociation constant ( $pA_2$ ) for each test compound at  $\alpha_1$ -  
15 adrenergic receptors are estimated for both aortic tissue and urinary bladder tissue.

$\alpha_1$ -Adrenergic Receptor *In Vitro*, Functional Assay in Tissue Isolated from Human: Human arterial blood vessels are obtained post-mortem and immediately immersed in cold physiological saline solution. Within 24 hours of removal, the isolated arterial tissue is placed in Krebs' solution (see above). The  
20 arteries are dissected free from extraneous tissue and then cut into cross-sectional rings approximately 3 mm in length. The arterial rings are suspended vertically in 10 mL tissue baths and bathed in Krebs' solution maintained at 37°C and constantly aerated with a 95% O<sub>2</sub>:5% CO<sub>2</sub> gas mixture. A resting tension (preload) of 1 to 1.5 g is applied to each ring and thereafter periodically readjusted to maintain a 1 g resting  
25 tension throughout the duration of the assay.

Human prostatic and bladder neck smooth muscle tissue is obtained following radical cystoprostatectomies or radical prostatectomies and immediately immersed in Krebs' solution. The prostatic and bladder tissue is dissected free from extraneous tissue and then strips of tissue 0.8 to 1.2 cm in length and 3 to 5 mm in width are cut  
30 and suspended vertically in 10 mL tissue baths and bathed in Krebs' solution maintained at 37°C and constantly aerated with a 95% O<sub>2</sub>:5% CO<sub>2</sub> gas mixture. A

resting tension (preload) of 0.75 to 1 g is applied to each muscle strip and thereafter periodically readjusted to maintain a 1 g resting tension throughout the duration of the assay.

The arterial ring and prostatic and bladder neck strip preparations are  
5 allowed to equilibrate for 60 minutes during which period the bath solution is replaced every 15 minutes. The tissue is then exposed to bath solution containing norepinephrine (1 to 10  $\mu$ M) and once a steady state contraction is produced the tissue is exposed to bath solution free of norepinephrine, replacing the solution  
10 twice every 5 minutes for 30 minutes. The arterial ring and prostatic and bladder neck strip preparations are exposed to norepinephrine in a cumulative concentration fashion. That is, the isolated tissue is exposed to bath solution containing a threshold concentration of norepinephrine until a steady state contractile response is attained and then the concentration of norepinephrine is cumulatively increased by  
0.5 log increments until a maximal or near maximal response is attained.

15 The tissue is then exposed to solution free of norepinephrine, replacing the solution twice every 5 minutes for 30 minutes. After baseline tension is established and readjusted to 1 g, the tissue is exposed to bath solution containing the test compound, replacing the solution every 15 minutes for 60 minutes. In the presence of the test compound, the tissue is again exposed to norepinephrine in a cumulative  
20 concentration fashion, increasing the norepinephrine concentration until a maximal or near maximal response is achieved.

The concentration ratio (CR) of norepinephrine necessary to produce equiactive responses in the absence and presence of the test compound is determined. Relying on the concentration ratio, the assay concentration (molar) of the  
25 test compound, and the relationship

$$pA_2 = -\log([test\ compound]/(CR-1))$$

the negative log of the dissociation constant ( $pA_2$ ) for each test compound at  $\alpha_1$ -adrenergic receptors are estimated for the arterial ring and prostatic and bladder neck strip preparations.

30 Preferred compounds of this invention demonstrate selectivity for the  $\alpha_{1B}$ -adrenoceptor subtype over the  $\alpha_{1A}$ - and  $\alpha_{1D}$ -adrenoceptor

- 57 -

subtypes. In contrast to non-subtype-selective  $\alpha_1$ -adrenoceptor antagonists, the  $\alpha_{1B}$ -adrenoceptor selective antagonist compounds of this invention do not demonstrate any significant cardiovascular effects *in vivo* at therapeutically effective doses. The compounds of this invention can selectively reduce or  
5 alleviate urinary tract disorders or symptoms, or ameliorate nociceptive and/or neurogenic pain, without producing the blood pressure lowering effects and/or the postural hypotension that are associated with previously described  $\alpha_1$ -adrenoceptor antagonists.

10

### EXAMPLES

The following preparations and examples are given to enable those skilled in the art to more clearly understand and practice the present invention. They should not be considered as limiting the scope of the invention, but merely as  
15 being illustrative and representative thereof.

#### Example 1

##### Furan-2-carboxylic acid methyl-(6-methylamino-hexyl)-amide 10

20 In accordance with the general Scheme 2B, the following is the preparation of a compound of Structure 4B, wherein each of  $R^{2a}$  and  $R^{2b}$  are methyl,  $R^{2c}$  is hydrogen,  $m = 6$ ; and Y is furan-2-carbonyl.

A solution of di-*tert*-butyl dicarbonate (7.85 g, 36 mmol) in dichloromethane (100 mL) was added to a solution of N,N'-dimethyl-1,6-  
25 hexanediamine (7.2 g, 50 mmol) in dichloromethane (250 mL) solution at  $-78^\circ\text{C}$  under nitrogen. After addition was complete, the cool-bath was removed and the resulting mixture was stirred (6 h) and warmed up to room temperature. The reaction mixture was washed with water (120 mL), the dichloromethane layer was separated, dried over anhydrous magnesium sulfate, filtered and  
30 concentrated under reduced pressure. The residue was purified by chromatography on silica gel (eluent dichloromethane:methanol:  $\text{Et}_3\text{N}$  90:8:2) to yield N-*tert*-butoxycarbonyl-N,N'-dimethyl-1,6-hexanediamine.



- 58 -

2-Furanoyl chloride (3.75 mL, 38 mmol) was added dropwise, at 0° C, to a mixture of N-*tert*-butoxycarbonyl-N,N'-dimethyl-1,6-hexanediamine (9.3 g, 38 mmol) and triethylamine (8.4 mL, 60 mmol) in dichloromethane (120 mL). The resulting mixture was stirred (2 h). The reaction mixture was washed with water (2 x 20 mL), brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The residue was treated with 50% trifluoroacetic acid/dichloromethane (100 mL) overnight. Trifluoroacetic acid and dichloromethane were removed under reduced pressure and the residue was azeotroped with toluene (50 mL). The residue was dissolved in dichloromethane (120 mL), treated carefully with excess NaHCO<sub>3</sub> (aqueous), the organic layer separated and the aqueous layer extracted with dichloromethane (2 x 50 mL). The combined organic layers were washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After removing the solvent, the residue was dried under vacuum to give the desired product **10** (7.8 g). MH<sup>+</sup> 239.2, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.50 (s, 1H), 7.0 (d, 1H), 6.50 (d, 1H), 3.55 (br. s, 3H), 3.0-3.3 (m, 4H), 2.4 5(s, 3H), 1.35-1.75 (m, 8H).

Similarly, substituting N,N-dimethyl-1,6-hexanediamine with a diamine, as described in Formulas (A), (B) and/or (C) herein, and following the procedure described in Example 1 the following compounds were prepared:

Furan-2-yl-(octahydro-quinoxalin-1-yl)-methanone **12** (MH<sup>+</sup> 235);  
[1,4]Diazepan-1-yl-furan-2-yl-methanone **14** (MH<sup>+</sup> 195);  
Furan-2-yl-piperazin-1-yl-methanone **16** (MH<sup>+</sup> 181);  
Furan-2-carboxylic acid methyl-(2-methylamino-ethyl)-amide **18** (MH<sup>+</sup> 183); and  
(2,5-Dimethyl-piperazin-1-yl)-furan-2-yl-methanone **20** (MH<sup>+</sup> 281).

### Example 2

#### 4-[4-(Furan-2-carbonyl)-piperazin-1-ylmethylene]- 2-naphthalen-1-yl-4H-oxazol-5-one **22**

In accordance with the general Scheme 2A, the following is the preparation of a compound of Structure 5A, wherein each of R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> is hydrogen, m = 2, n = 1; Z is N; Y is furan-2-carbonyl; and R<sup>1</sup> is naphthyl.

A 0.25 M acetonitrile solution of 4-ethoxymethylene-2-naphthalen-1-yl-4H-oxazol-5-one (200  $\mu$ L) was added to a 0.25 M acetonitrile solution of 1-(2-furanoyl)piperazine (200  $\mu$ L). The reaction vessel was sealed and the mixture shaken at 55° C overnight. The volatile materials were removed under reduced  
5 pressure to yield the desired product **22** ( $MH^+$  402).

Similarly, substituting 1-(2-furanoyl)piperazine with other amines prepared using Example 1, and 4-ethoxymethylene-2-naphthalen-1-yl-4H-oxazol-5-one with other oxazolones, utilizing the procedure described in Example 2 the following compounds were prepared:

10 Furan-2-carboxylic acid methyl-{6-[methyl-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-amino]-hexyl}-amide **24** ( $MH^+$  460);

4-[4-(Furan-2-carbonyl)-octahydro-quinoxalin-1-ylmethylene]-2-(3-methoxy-phenyl)-4H-oxazol-5-one **26** ( $MH^+$  436);

4-[4-(Furan-2-carbonyl)-2,5-dimethyl-piperazin-1-ylmethylene]-2-  
15 naphthalen-1-yl-4H-oxazol-5-one **28** ( $MH^+$  430);

Furan-2-carboxylic acid (6-[[2-(3-methoxy-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-methyl-amino]-hexyl)-methyl-amide **30** ( $MH^+$  440);

4-[4-(Furan-2-carbonyl)-octahydro-quinoxalin-1-ylmethylene]-2-m-tolyl-4H-oxazol-5-one **32** ( $MH^+$  420);

20 Furan-2-carboxylic acid methyl-{6-[methyl-(5-oxo-2-m-tolyl-oxazol-4-ylidenemethyl)-amino]-hexyl}-amide **34** ( $MH^+$  424);

Furan-2-carboxylic acid (6-[[2-(2-chloro-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-methyl-amino]-hexyl)-methyl-amide **36** ( $MH^+$  444);

Furan-2-carboxylic acid (6-[[2-(4-chloro-phenyl)-5-oxo-oxazol-4-  
25 ylidenemethyl]-methyl-amino]-hexyl)-methyl-amide **38** ( $MH^+$  444);

Furan-2-carboxylic acid methyl-{6-[methyl-(5-oxo-2-phenyl-oxazol-4-ylidenemethyl)-amino]-hexyl}-amide **40** ( $MH^+$  410);

4-[4-(Furan-2-carbonyl)-2,5-dimethyl-piperazin-1-ylmethylene]-2-naphthalen-2-yl-4H-oxazol-5-one **42** ( $MH^+$  430);

30 Furan-2-carboxylic acid methyl-(6-{methyl-[5-oxo-2-(2-trifluoromethyl-phenyl)-oxazol-4-ylidenemethyl]-amino}-hexyl)-amide **44** ( $MH^+$  478);

Furan-2-carboxylic acid methyl-{6-[methyl-(5-oxo-2-o-tolyl-oxazol-4-ylidenemethyl)-amino]-hexyl}-amide **46** ( $MH^+$  424); and

2-Biphenyl-4-yl-4-[4-(furan-2-carbonyl)-[1,4]diazepan-1-ylmethylene]-4H-oxazol-5-one **48** ( $MH^+$  442).

5

### Example 3

#### 2-Naphthalen-1-yl-4-piperazin-1-ylmethylene-4H-oxazol-5-one 50

In accordance with the general Scheme 3A, the following is the  
10 preparation of a compound of Structure 8A, wherein each of  $R^{2a}$ ,  $R^{2b}$  and  $R^{2c}$  is hydrogen,  $m = 2$ ,  $n = 1$ ; Z is NH; and  $R^1$  is naphthyl.

A mixture of 4-ethoxymethylene-2-naphthalen-1-yl-4H-oxazol-5-one (4.0 g, 15 mmol) and N-*tert*-butoxycarbonyl-piperazine (2.8 g, 15 mmol) was refluxed in acetonitrile for 4 h. The reaction mixture was cooled to room temperature and  
15 the resulting yellow solid product (5.7 g) was collected by filtration. The yellow solid was then treated with 50% trifluoroacetic acid/dichloromethane (100 mL) overnight at room temperature, the solvents were removed under reduced pressure and the residue was azeotroped with toluene (50 mL). The residue was suspended in dichloromethane (100 mL) and aqueous  $NaHCO_3$  (20 mL), the  
20 phases were separated and the aqueous layer was extracted further with dichloromethane (3 x 100 mL). The combined organic layers were dried over  $Na_2SO_4$  and concentrated to yield the desired product **50** as a pale yellow solid (3.0 g).  $MH^+$  308.1,  $^1H$  NMR: ( $CDCl_3$ )  $\delta$  9.20 (d, 1H), 8.35 (d, 1H), 8.05 (m, 2H), 7.7 (m, 3H), 7.30 (s, 1H), 4.60 (m, 2H), 3.70 (m, 2H), 3.25 (m, 4H).

25 Similarly, substituting N-*tert*-butoxycarbonyl-piperazine with other suitably mono-protected diamines prepared using Example 1, and 4-ethoxymethylene-2-naphthalen-1-yl-4H-oxazol-5-one with other oxazolones, following the procedure described in Example 3, the following compounds were prepared:

2-Naphthalen-1-yl-4-(octahydro-quinoxalin-1-ylmethylene)-4H-oxazol-5-one **52** ( $MH^+$  362);  
30

4-{[Methyl-(6-methylamino-hexyl)-amino]-methylene}-2-naphthalen-1-yl-4H-oxazol-5-one **54** ( $MH^+$  366);

4-[1,4]Diazepan-1-ylmethylene-2-naphthalen-1-yl-4H-oxazol-5-one **56**  
(MH<sup>+</sup> 322);

2-(3-Methoxy-phenyl)-4-piperazin-1-ylmethylene-4H-oxazol-5-one **58**  
(MH<sup>+</sup> 288);

2-(3-Methoxy-phenyl)-4-(octahydro-quinoxalin-1-ylmethylene)-4H-oxazol-  
5-one **60** (MH<sup>+</sup> 342);

2-(3-Methoxy-phenyl)-4-[[methyl-(6-methylamino-hexyl)-amino]-  
methylene]-4H-oxazol-5-one **62** (MH<sup>+</sup> 346); and

4-[1,4]Diazepan-1-ylmethylene-2-(3-methoxy-phenyl)-4H-oxazol-5-one **64**  
(MH<sup>+</sup> 302).

#### Example 4

#### 4-[4-(Furan-2-carbonyl)-piperazin-1-ylmethylene]-2-naphthalen- 1-yl-4H-oxazol-5-one **66**

In accordance with the general Scheme 3A, the following is the  
preparation of a compound of Structure 5A, wherein each of R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> is  
hydrogen, m = 2, n = 1; Z is N; Y is furan-2-carbonyl; and R<sup>1</sup> is naphthyl.

To a 0.125 M solution of **50**, prepared as described in Example 3 (400 µL,  
50 µmole), in methylene chloride was added a 1.25 M acetonitrile solution of  
Hünig's base (50 µL) followed by a 0.25 M solution of 2-furanoyl chloride in  
acetonitrile (200 µL, 50 µmole). The reaction vessel sealed, and the resulting  
mixture shaken at room temperature for 24 h. The solvent was removed to yield  
the desired product **66** (MH<sup>+</sup> 402).

Similarly, substituting 2-furanoyl chloride with other acid chlorides, and **50**  
prepared as described in Example 3 with other oxazolones, following the  
procedure described in Example 4, the following compounds were prepared:

Furan-2-carboxylic acid methyl-{6-[methyl-(2-naphthalen-1-yl-5-oxo-  
oxazol-4-ylidenemethyl)-amino]-hexyl}-amide **68** (MH<sup>+</sup> 460);

2-(3-Methoxy-phenyl)-4-[4-(3-methyl-benzoyl)-octahydro-quinoxalin-1-  
ylmethylene]-4H-oxazol-5-one **70** (MH<sup>+</sup> 460);

4-[4-(Furan-2-carbonyl)-octahydro-quinoxalin-1-ylmethylene]-2-naphthalen-1-yl-4H-oxazol-5-one **72** ( $MH^+$  456);

Furan-2-carboxylic acid (6-[[2-(3-methoxy-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-methyl-amino]-hexyl)-methyl-amide **74** ( $MH^+$  440);

5        2-Naphthalen-1-yl-4-[4-(2-thiophen-2-yl-acetyl)-piperazin-1-ylmethylene]-4H-oxazol-5-one **76** ( $MH^+$  432);

4-[4-(3-Methyl-butyryl)-piperazin-1-ylmethylene]-2-naphthalen-1-yl-4H-oxazol-5-one **78** ( $MH^+$  392);

2-Naphthalen-1-yl-4-(4-phenylacetyl-[1,4]diazepan-1-ylmethylene)-4H-oxazol-5-one **80** ( $MH^+$  440);

2-(3-Methoxy-phenyl)-4-[4-(2-trifluoromethyl-benzoyl)-octahydro-quinoxalin-1-ylmethylene]-4H-oxazol-5-one **82** ( $MH^+$  514);

4-(4-Cyclohexanecarbonyl-piperazin-1-ylmethylene)-2-naphthalen-1-yl-4H-oxazol-5-one **84** ( $MH^+$  418);

15        3,N-Dimethyl-N-{6-[methyl-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-amino]-hexyl}-butyramide **86** ( $MH^+$  450);

2-(3-Methoxy-phenyl)-4-[4-(4-methyl-benzoyl)-octahydro-quinoxalin-1-ylmethylene]-4H-oxazol-5-one **88** ( $MH^+$  460);

4-[4-(2-Chloro-benzoyl)-octahydro-quinoxalin-1-ylmethylene]-2-(3-methoxy-phenyl)-4H-oxazol-5-one **90** ( $MH^+$  480);

20        4-(4-Isobutyryl-piperazin-1-ylmethylene)-2-naphthalen-1-yl-4H-oxazol-5-one **92** ( $MH^+$  378);

2-Chloro-N-methyl-N-{6-[methyl-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-amino]-hexyl}-benzamide **94** ( $MH^+$  504);

25        2-(3-Methoxy-phenyl)-4-[4-(3-methyl-butyryl)-octahydro-quinoxalin-1-ylmethylene]-4H-oxazol-5-one **96** ( $MH^+$  426);

4-[4-(2,4-Difluoro-benzoyl)-octahydro-quinoxalin-1-ylmethylene]-2-(3-methoxy-phenyl)-4H-oxazol-5-one **98** ( $MH^+$  482);

4-[4-(Furan-2-carbonyl)-octahydro-quinoxalin-1-ylmethylene]-2-(3-methoxy-phenyl)-4H-oxazol-5-one **100** ( $MH^+$  436);

30        2-Naphthalen-1-yl-4-[4-(pyridine-4-carbonyl)-piperazin-1-ylmethylene]-4H-oxazol-5-one **102** ( $MH^+$  413);

N-Methyl-N-{6-[methyl-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-amino]-hexyl}-2-trifluoromethyl-benzamide **104** ( $MH^+$  538); and

4-[4-(2-Fluoro-benzoyl)-octahydro-quinoxalin-1-ylmethylene]-2-(3-methoxy-phenyl)-4H-oxazol-5-one **106** ( $MH^+$  464).

5

### Example 5

#### 4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid (3-fluoro-phenyl)-amide **108**

10 In accordance with the general Scheme 3A, the following is the preparation of a compound of Structure 5A, wherein each of  $R^{2a}$ ,  $R^{2b}$  and  $R^{2c}$  is hydrogen,  $m = 2$ ,  $n = 1$ ; Z is N; Y is (3-fluoro-phenyl)-amide; and  $R^1$  is naphthyl.

To a 0.125 M solution of **50**, prepared as described in Example 3 (400  $\mu$ L, 50  $\mu$ mole), in methylene chloride was added a 0.25 M acetonitrile solution of 3-fluoro-phenyl isocyanate (200  $\mu$ L, 50  $\mu$ mole). The reaction vessel was sealed and the mixture shaken at room temperature for 24 h. Removal of the volatile materials under high vacuum yielded the desired product **108** ( $MH^+$  445).

Similarly, substituting 3-fluoro-phenyl isocyanate with other isocyanates and, prepared as described in Example 3, with other oxazolones, following the procedure described in Example 5, the following compounds were prepared:

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid m-tolylamide **110** ( $MH^+$  441);

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid (3-chloro-phenyl)-amide **112** ( $MH^+$  461);

25 4-[2-(3-Methoxy-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide **114** ( $MH^+$  407);

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid (3-methoxy-phenyl)-amide **116** ( $MH^+$  457);

30 4-[2-(3-Methoxy-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid (3-chloro-phenyl)-amide **118** ( $MH^+$  441);

4-[2-(3-Methoxy-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid m-tolylamide **120** ( $MH^+$  421);

4-[2-(3-Methoxy-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid (3-fluoro-phenyl)-amide **122** ( $MH^+$  425);

4-[2-(3-Methoxy-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenethyl-amide **124** ( $MH^+$  435);

5 4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-[1,4]diazepane-1-carboxylic acid (3-fluoro-phenyl)-amide **126** ( $MH^+$  459);

1-Methyl-1-{6-[methyl-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-amino]-hexyl}-3-m-tolyl-urea **128** ( $MH^+$  499);

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid cyclohexylamide **130** ( $MH^+$  433);

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid isopropylamide **132** ( $MH^+$  393);

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid ethylamide **134** ( $MH^+$  379);

15 4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid tert-butylamide **136** ( $MH^+$  407);

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid allylamide **138** ( $MH^+$  391);

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid (2-ethoxy-phenyl)-amide **140** ( $MH^+$  471);

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid (2-fluoro-phenyl)-amide **142** ( $MH^+$  445);

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid (3-cyano-phenyl)-amide **144** ( $MH^+$  452);

25 4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid (tetrahydro-pyran-2-yl)-amide **146** ( $MH^+$  435); and

3-[[4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carbonyl]-amino]-propionic acid ethyl ester **148** ( $MH^+$  451).

Example 62-Naphthalen-1-yl-4-[4-(quinoline-8-sulfonyl)-piperazin-1-ylmethylene]-  
4H-oxazol-5-one 150

5 In accordance with the general Scheme 3A, the following is the preparation of a compound of Structure 5A, wherein each of R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> is hydrogen, m = 2, n = 1; Z is N; Y is quinoline-8-sulfonyl; and R<sup>1</sup> is naphthyl.

To a 0.125 M solution of **50**, prepared as described in Example 3 (400 µL, 50 µmole), in methylene chloride was added a 1.25 M acetonitrile solution of  
10 Hünig's base (50 µL). A 0.25 M solution of 8-quinolinylsulfonyl chloride in acetonitrile (200 µL, 50 µmole) was added, the reaction vessel sealed and the resulting mixture shaken at room temperature for 24 h. The solvent was removed to yield the desired product **150** (MH<sup>+</sup> 498).

Similarly, substituting 8-quinolinylsulfonyl chloride with other sulfonyl  
15 chlorides, and **50**, prepared as described in Example 3, with other oxazolones, following the procedure described in Example 6, the following compounds were prepared:

N-Methyl-N-{6-[methyl-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-amino]-hexyl}-methanesulfonamide **152** (MH<sup>+</sup> 444);

20 N-[4-(Methyl-{6-[methyl-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-amino]-hexyl}-sulfamoyl)-phenyl]-acetamide **154** (MH<sup>+</sup> 562);

2-Naphthalen-1-yl-4-[4-(quinoline-8-sulfonyl)-[1,4]diazepan-1-ylmethylene]-4H-oxazol-5-one **156** (MH<sup>+</sup> 513);

4-(4-Benzenesulfonyl-[1,4]diazepan-1-ylmethylene)-2-naphthalen-1-yl-4H-  
25 oxazol-5-one **158** (MH<sup>+</sup> 461);

4-(4-Methanesulfonyl-[1,4]diazepan-1-ylmethylene)-2-naphthalen-1-yl-4H-oxazol-5-one **160** (MH<sup>+</sup> 400);

4,Dimethyl-N-{6-[methyl-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-amino]-hexyl}-benzenesulfonamide **162** (MH<sup>+</sup> 520);

30 4-Chloro-N-methyl-N-{6-[methyl-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-amino]-hexyl}-benzenesulfonamide **164** (MH<sup>+</sup> 540);



N-Methyl-N-{6-[methyl-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-amino]-hexyl}-benzenesulfonamide **166** ( $\text{MH}^+$  506);

N-(6-[[2-(3-Methoxy-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-methyl-amino]-hexyl)-N-methyl-methanesulfonamide **168** ( $\text{MH}^+$  424);

5        5-Dimethylamino-naphthalene-1-sulfonic acid methyl-{6-[methyl-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-amino]-hexyl}-amide **170** ( $\text{MH}^+$  598); and

4-Methoxy-N-methyl-N-{6-[methyl-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-amino]-hexyl}-benzenesulfonamide **172** ( $\text{MH}^+$  536).

10

#### Example 7

#### 4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid isopropyl ester **174**

15        In accordance with the general Scheme 3A, the following is the preparation of a compound of Structure 5A, wherein each of  $\text{R}^{2a}$ ,  $\text{R}^{2b}$  and  $\text{R}^{2c}$  is hydrogen,  $m = 2$ ,  $n = 1$ ; Z is N; Y is isopropoxycarbonyl; and  $\text{R}^1$  is naphthyl.

To a 0.125 M solution of **50**, prepared as described in Example 3 (400  $\mu\text{L}$ , 50  $\mu\text{mole}$ ), in methylene chloride was added a 1.25 M acetonitrile solution of  
20        Hünig's base (50  $\mu\text{L}$ ). A 0.25 M solution of isopropyl chloroformate in acetonitrile (200  $\mu\text{L}$ , 50  $\mu\text{mole}$ ) was added the reaction vessel sealed and the resulting mixture shaken at room temperature for 24 h. The solvent was removed to yield the desired product **174** ( $\text{MH}^+$  394).

Similarly, substituting isopropyl chloroformate with other chloroformates,  
25        and **50**, prepared as described in Example 3 with other oxazolones, following the procedure described in Example 7, the following compounds were prepared:

Methyl-{6-[methyl-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-amino]-hexyl}-carbamic acid methyl ester **176** ( $\text{MH}^+$  424);

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-  
30        carboxylic acid isopropyl ester **178** ( $\text{MH}^+$  394);

(6-[[2-(3-Methoxy-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-methyl-amino]-hexyl)-methyl-carbamic acid cyclopentyl ester **180** ( $\text{MH}^+$  458);

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid cyclopentyl ester **182** ( $MH^+$  420);

Methyl-{6-[methyl-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-amino]-hexyl}-carbamic acid cyclopentyl ester **184** ( $MH^+$  478);

5 (6-[[2-(3-Methoxy-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-methyl-amino]-hexyl)-methyl-carbamic acid methyl ester **186** ( $MH^+$  404);

Methyl-{6-[methyl-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-amino]-hexyl}-carbamic acid isobutyl ester **188** ( $MH^+$  466);

10 (6-[[2-(3-Methoxy-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-methyl-amino]-hexyl)-methyl-carbamic acid isobutyl ester **190** ( $MH^+$  446);

Methyl-{6-[methyl-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-amino]-hexyl}-carbamic acid p-tolyl ester **192** ( $MH^+$  500); and

(6-[[2-(3-Methoxy-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-methyl-amino]-hexyl)-methyl-carbamic acid isopropyl ester **194** ( $MH^+$  432).

15

### Example 8

#### Piperazine-1-carboxylic acid phenylamide trifluoroacetate **196**

In accordance with the general Scheme 2A, the following is the  
20 preparation of a compound of Structure 4A, wherein each of  $R^{2a}$ ,  $R^{2b}$  and  $R^{2c}$  is hydrogen,  $m = 2$ ,  $n = 1$ ; Z is N; and Y is N-phenylamide.

Phenyl isocyanate (3.50 g, 29.7 mmol) was added to a solution of N-tert-butoxycarbonyl-piperazine (5.03 g, 27 mmol) in acetonitrile. The mixture was refluxed (90 min), cooled to room temperature and evaporated under reduced  
25 pressure to yield a white solid (8.0 g). The resulting solid was dissolved in dichloromethane (15 mL), cooled to 0° C, and trifluoroacetic acid (15 mL) was added. The solution was stirred (2 h) and evaporated under reduced pressure to yield the desired product as its trifluoroacetate salt **196**, as a clear colorless oil that crystallized on standing.  $^1H$  NMR: (DMSO  $d_6$ )  $\delta$  9.00 (s, 2H, exch.  $D_2O$ ),  
30 8.75 (s, 1H exch.  $D_2O$ ), 7.45 (m, 2H), 7.21 (m, 2H), 7.00 (m, 1H), 3.66 (m, 4H), 3.14 (m, 4H).

Example 92-Benzyl-octahydro-pyrrolo[3,4-c]pyrrole 198

In accordance with the general Scheme 2C, the following is the  
5 preparation of a compound of Structure 4C, wherein each of p, q, r and s = 1;  
and Y is benzyl.

Triethylamine (16.2 g, 0.16 mol) was added to a suspension of N-  
benzylmaleimide (25.0 g, 0.13 mol), N-benzylglycine hydrochloride (32.3 g, 0.16  
mol) and paraformaldehyde (25.2 g, 0.84 mol) in benzene (1 L) in a mechanically  
10 stirred flask, under a nitrogen atmosphere. The resulting solution was refluxed  
(3.5 h), cooled to room temperature, dried over anhydrous magnesium sulfate,  
treated with decolorizing charcoal, filtered through Celite and evaporated under  
reduced pressure. The residue (52.9 g) was dissolved in 1,2-dichloroethane,  
and under a nitrogen atmosphere, sodium bicarbonate (22.4 g, 0.26 mol) was  
15 added followed by dropwise addition of 1-chloroethylchloroformate (38.18 g, 0.26  
mol). The resulting mixture was refluxed overnight before cooling to room  
temperature. The solution was dried over anhydrous magnesium sulfate, treated  
with decolorizing charcoal, filtered through Celite and evaporated under reduced  
pressure. The residue was dissolved in anhydrous methanol (500 mL) and  
20 heated at 50° C for 3 h. On cooling to room temperature the solution was  
concentrated to approximately half its volume yielding a precipitate. The solid  
was collected by filtration, washed on the filter with diethyl ether and dried under  
vacuum yielding a white crystalline solid (26.0 g).

A solution of the above mentioned solid (25.9 g) in tetrahydrofuran (250  
25 mL) was added dropwise under a nitrogen atmosphere (over 1 h) to a solution of  
lithium aluminum hydride (1.0 M in tetrahydrofuran, 300 mL, 300 mmol) in  
tetrahydrofuran (200 mL) cooled to 0° C. The resulting slurry was warmed  
slowly, refluxed for 15 min, cooled and stirred overnight at room temperature.  
Water (11.3 mL) was added very carefully with stirring followed by 15% aqueous  
30 NaOH (11.3 mL). Additional water (34.1 mL) was added followed by anhydrous  
magnesium sulfate, and the mixture was stirred at room temperature, filtered  
through Celite and evaporated under reduced pressure to yield the desired

product as a yellow oil **198** (18.7 g). <sup>1</sup>H NMR: (CDCl<sub>3</sub>) δ 7.36-7.19 (m, 5H), 3.51 (s, 2H), 2.89-2.57 (m, 8H), 2.35-2.27 (m, 2H), 2.01 (br. s, 1H, exch. D<sub>2</sub>O).

#### Example 10.

##### Hexahydro-pyrrolo[3,4-c]pyrrole-2-carboxylic acid phenylamide **200**

In accordance with the general Scheme 2C, the following is the preparation of a compound of Structure 4C, wherein each of p, q, r and s = 1; and Y is N-phenylamide.

10 To a solution of **198** (250 mg, 1.2 mmol), prepared as described in Example 9, in dichloromethane (5 mL) at 0° C, under a nitrogen atmosphere, was added N,N-diisopropylethylamine (175 mg, 1.4 mmol) followed by phenyl isocyanate (147 mg, 1.2 mmol). The reaction mixture was stirred at 0° C for 4 h, diluted with dichloromethane (25 mL), washed with saturated aqueous  
15 ammonium chloride solution (5 mL), water (5 mL), and brine (5 mL), dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. Flash chromatography of the residue over silica gel (eluent dichloromethane:methanol, 93:7) yielded a white solid (247 mg).

To a solution of the resulting white solid (243 mg, 7.7 mmol) in ethanol (20  
20 mL), ammonium formate (290 mg, 4.6 mmol) was added, followed by 10% palladium on activated carbon (100mg) and the mixture was refluxed for 5 h. On cooling to room temperature, the mixture was filtered through Celite to yield the desired product as a white solid **200** (211 mg). <sup>1</sup>H NMR: (DMSO d<sub>6</sub>) δ 8.40 (br. s, 1H, exch. D<sub>2</sub>O), 7.56 (m, 2H), 7.28 (m, 2H), 7.00 (m, 1H), 3.74-2.96 (m, 10H).

25

#### Example 11

##### Piperazine-1-carboxylic acid pyridin-2-ylamide trifluoroacetate **202**

In accordance with the general Scheme 2A, the following is the  
30 preparation of a compound of Structure 4A, wherein each of R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> is hydrogen, m = 2, n = 1; Z is N; and Y is N-pyridin-2-ylamide.

To a solution of 2-aminopyridine (2.50 g, 26.6 mmol) and triethylamine (4.05 mL) in dichloromethane (25 mL), cooled to -20° C, was added phenyl chloroformate (3.65 mL, 29.2 mmol). The mixture was stirred at -20° C for 1 h, warmed up to room temperature and washed with aqueous solution of saturated  
5 NaHCO<sub>3</sub> (100 mL). The organic phase was separated, dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to yield a pale yellow solid (6.05 g).

To a solution of the resulting pale yellow solid (5.57 g, 26 mmol) in DMF (100 mL), triethylamine (3.80 mL, 27.5 mmol) was added, followed by *N*-*tert*-  
10 butoxycarbonyl-piperazine (5.1 g, 27.5 mmol). The mixture was heated at 100° C for 1 hour, cooled to room temperature and evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel (eluent hexane:ethyl acetate 50:50) to yield a white solid (4.15 g).

The resulting white solid (4.0 g, 13 mmol) was dissolved in 1:1  
15 trifluoroacetic acid:dichloromethane and the mixture stirred at room temperature for 2 h before removal of the volatile materials by evaporation under reduced pressure. Recrystallization of the residue from ethanol/diethyl ether yielded the trifluoroacetic acid salt of the desired product as a white solid **202** (5.02 g). <sup>1</sup>H NMR: (DMSO d<sub>6</sub>) δ 9.02 (br. s, 1H, exch. D<sub>2</sub>O), 8.28 (m, 1H), 7.84 (m, 1H), 7.75  
20 (m, 1H), 7.10 (m, 1H), 3.69 (m, 4H), 3.15 (m, 4H).

Similarly, replacing 2-aminopyridine with 4-aminopyridine and following the procedure outlined in Example 11 the trifluoroacetate salt of piperazine-1-carboxylic acid pyridin-4-ylamide **204** was obtained as a thick syrup. <sup>1</sup>H NMR: (DMSO d<sub>6</sub>) δ 9.37 (s, 2H), 8.85 (m, 2H), 8.18 (m, 2H), 3.98 (m, 4H), 3.44 (m,  
25 4H).

### Example 12

#### Piperazine-1-carboxylic acid pyridin-3-ylamide trifluoroacetate **206**

30 In accordance with the general Scheme 2A, the following is the preparation of a compound of Structure 4A; wherein each of R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> is hydrogen, m = 2, n = 1; Z is N; and Y is N-pyridin-3-ylamide.

- 71 -

Cold concentrated aqueous HCl (2.43 mL) was added to nicotinyldiazide (2.0 g, 15.6 mmol) cooled to 0° C in an ice bath. To the resulting mixture a solution of sodium nitrite (2.0 g, 29.1 mmol) in water (3.3 mL) was added dropwise. On completion of addition a green solution was formed. The solution was extracted with diethyl ether (2 x 30 mL) and the aqueous phase neutralized carefully with solid sodium bicarbonate. The resulting basic solution was extracted with diethyl ether (2 x 20 mL), the ether extracts combined, washed with aqueous saturated NaHCO<sub>3</sub>, dried over CaCl<sub>2</sub>/CaSO<sub>4</sub> for 30 min and evaporated under reduced pressure without warming to yield a residue. The residue was dissolved in toluene (43 mL) and refluxed for 80 min, cooled to room temperature, added to a solution of N-*tert*-butoxycarbonyl-piperazine (1.5 g, 8.3 mmol) in dichloromethane (43 mL) and stirred at room temperature overnight. The resulting yellow solution was evaporated under reduced pressure and the residue purified by flash chromatography over silica gel (eluent dichloromethane: methanol, 95:5) to yield a pale yellow solid (1.94 g).

Trifluoroacetic acid (8 mL) was added to a solution of the pale yellow solid (1.90 g) in dichloromethane (8 mL). The reaction mixture was stirred at room temperature for 1 h and evaporated to yield the trifluoroacetic acid salt of the desired product **206** (4.20 g). <sup>1</sup>H NMR: (DMSO d<sub>6</sub>) δ 9.67 (s, 1H), 9.02 (m, 1H), 8.50 (m, 1H), 8.38 (m, 1H), 7.88 (m, 1H), 3.71 (m, 4H), 3.18 (m, 4H).

### Example 13

#### 4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-

#### 1-carboxylic acid phenylamide **208**

In accordance with the general Scheme 2A, the following is the preparation of a compound of Structure 5A, wherein each of R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> is hydrogen, m = 2, n = 1; Z is N; Y is N-phenylamide; and R<sup>1</sup> is naphthyl.

A 0.1 M solution of 4-ethoxymethylene-2-naphthalen-1-yl-4H-oxazol-5-one in DMSO (500 µL, 50 µmole) was added to a 0.15 M solution of **196** (333 µL, 50 µmole), prepared as described in Example 8. The reaction vessel was sealed

and the resulting mixture shaken at room temperature overnight to yield the desired product as a DMSO solution **208** ( $MH^+$  427).

Similarly, substituting 4-ethoxymethylene-2-naphthalen-1-yl-4H-oxazol-5-one with other oxazolones and following the procedure described in Example 13, the following compounds were prepared:

4-[2-(4-Fluoro-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide **212** ( $MH^+$  445);

4-(5-Oxo-2-quinolin-4-yl-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid phenylamide **214** ( $MH^+$  428);

10 4-[2-(3-Methoxy-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide **216** ( $MH^+$  407);

4-(2-Biphenyl-4-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid phenylamide **218** ( $MH^+$  453);

15 4-(5-Oxo-2-o-tolyl-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid phenylamide **220** ( $MH^+$  391);

4-[2-(1-Methyl-1H-indol-2-yl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide **222** ( $MH^+$  430);

4-(5-Oxo-2-m-tolyl-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid phenylamide **224** ( $MH^+$  391);

20 4-[2-(3-Methoxy-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide **226** ( $MH^+$  407);

4-[2-(2-Chloro-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide **228** ( $MH^+$  411);

25 4-[5-Oxo-2-(2-trifluoromethyl-phenyl)-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide **230** ( $MH^+$  445);

4-(5-Oxo-2-phenyl-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid phenylamide **232** ( $MH^+$  377);

4-(2-Benzo[b]thiophen-2-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid phenylamide **234** ( $MH^+$  433);

30 4-[5-Oxo-2-(3-trifluoromethyl-phenyl)-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide **236** ( $MH^+$  445);

4-[2-(2,3-Dichloro-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide **238** ( $\text{MH}^+$  445); and

4-[2-(2,4-Dichloro-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide **240** ( $\text{MH}^+$  445).

5

#### Example 14

##### 4-[2-(2,3-Dihydro-benzofuran-7-yl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide **242**

10 In accordance with the general Scheme 2A, the following is the preparation of a compound of Structure 5A, wherein each of  $\text{R}^{2a}$ ,  $\text{R}^{2b}$  and  $\text{R}^{2c}$  is hydrogen,  $m = 2$ ,  $n = 1$ ; Z is N; Y is N-phenylamide; and  $\text{R}^1$  is 2,3-dihydro-benzofuran-7-yl.

To a suspension of **196** (227 mg, 0.71 mmol), prepared as described in  
15 Example 8, and 2-(2,3-dihydro-benzofuranoyl-7-yl)-4-ethoxymethylene-4H-oxazol-5-one (185 mg, 0.71 mmol) in acetonitrile (5 mL), N,N-diisopropylethylamine (184 mg, 1.42 mmol) was added, and the mixture stirred at room temperature for 2 h. The desired product **242** (115 mg) was collected by filtration and dried under vacuum.  $\text{MH}^+$  419,  $^1\text{H}$  NMR: (DMSO  $d_6$ )  $\delta$  8.64 (s, 1H, 20  
exch.  $\text{D}_2\text{O}$ ), 7.22-7.58 (m, 7H), 6.95 (m, 2H), 4.65 (m, 2H), 4.38 (m, 2H), 3.67 (m, 2H), 3.38 (m, 4H), 3.19 (m, 2H).

Similarly, substituting **196** for other substituted amines, and 2-(2,3-dihydro-benzofuran-7-yl)-4-ethoxymethylene-4H-oxazol-5-one with other oxazolones, following the procedure described in Example 14, the following  
25 compounds were prepared:

4-[2-(4-Fluoro-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide **212**;  $\text{MH}^+$  445;  $^1\text{H}$  NMR (DMSO  $d_6$ )  $\delta$  9.30 (d, 1H), 8.68 (s, 1H), 8.15 (m, 2H), 7.78 (m, 2H), 7.50 (m, 4H), 7.28 (m, 1H), 6.98 (m, 1H), 4.45 (m, 2H), 3.70 (m, 6H);

30 4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid phenylamide **208**;  $\text{MH}^+$  427;  $^1\text{H}$  NMR: (DMSO  $d_6$ )  $\delta$  9.20 (d, 1H),



8.68 (s, 1H), 8.05 (m, 3H), 7.65 (m, 3H), 7.55 (s, 1H), 7.48 (d, 2H), 7.25 (t, 2H), 6.95 (t, 1H), 4.45 (m, 2H), 3.70 (m, 6H);

4-[2-(7-Fluorobenzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide **248**;  $MH^+$  435;  $^1H$  NMR (DMSO  $d_6$ )  $\delta$  8.73 (s, 1H, 5  
exch.  $D_2O$ ), 8.29 (d, 1H), 7.72 (m, 1H), 7.50 (m, 4H), 7.48 (m, 1H), 7.25 (m, 2H), 6.95 (m, 1H), 3.73 (m, 2H), 3.73 (m, 4H), 3.66 (m, 2H);

4-(2-Benzofuran-4-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid phenylamide **250**;  $MH^+$  416;  $^1H$  NMR (DMSO  $d_6$ )  $\delta$  8.67 (br. s, 1H, 10  
exch.  $D_2O$ ), 8.18 (d, 1H), 7.75 (m, 2H), 7.51 (m, 5H), 7.26 (m, 2H), 6.96 (m, 1H), 4.46 (m, 2H), 3.73 (m, 4H), 3.66 (m, 2H);

4-(2-Benzofuran-7-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid phenylamide **252** ( $MH^+$  417);

4-[2-(2,3-Dihydro-benzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide **254** ( $M^+$  418);

4-[2-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide **256** ( $MH^+$  435); 15

4-(2-Benzo[1,3]dioxol-4-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid phenylamide **258** ( $MH^+$  421);

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid pyridin-2-ylamide **260** ( $MH^+$  428); 20

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid pyridin-3-ylamide **262** ( $M^+$  427);

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid pyridin-4-ylamide **264** ( $MH^+$  428);

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid (3-cyano-phenyl)-amide **266** ( $MH^+$  452); 25

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid diphenylamide **268** ( $MH^+$  517);

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid tert-butylamide **270** ( $MH^+$  407); and 30

5-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-hexahydro-pyrrolo[3,4-c]pyrrole-2-carboxylic acid phenylamide **272** ( $MH^+$  453).

Example 15N-Pyridin-2-yl-piperazine-1-carboxamide trifluoroacetate 274

5 In accordance with the general Scheme 2A, the following is the preparation of a compound of Structure 4A, wherein each of  $R^{2a}$ ,  $R^{2b}$  and  $R^{2c}$  is hydrogen,  $m = 2$ ,  $n = 1$ ; Z is N; and Y is N-pyridin-2-yl-carboxamide.

A mixture of 1H-pyrrole-1-carboxamide hydrochloride (4.40 g, 30 mmol), N-*tert*-butoxycarbonyl-piperazine (5.59 g, 30 mmol) and N,N-  
10 diisopropylethylamine (6.3 mL, 36 mmol) in 2-propanol (50 mL) was refluxed for 24 h. The volatile materials were removed on a rotavapor, the residue suspended in acetonitrile (50 mL) and filtered. The precipitate was further washed with acetonitrile (50 mL) to yield a white solid (6.2 g).

To a solution of the resulting white solid (37.29 g, 163 mmol), in dioxane  
15 (500 mL) sodium hydride (60% dispersion in mineral oil, 16.3 g, 407 mmol) was added under a nitrogen atmosphere, followed by 2-fluoropyridine (15.8 g, 163 mmol). The resulting mixture was refluxed for 90 min, cooled to room temperature and stirred overnight. Water was added carefully to quench the excess sodium hydride, and all of the volatile materials removed by evaporation  
20 under reduced pressure. Purification of the residue by flash chromatography over silica gel (eluent dichloromethane:methanol:NH<sub>4</sub>OH, 95:5:0.5) yielded a pale solid (16.0 g).

Trifluoroacetic acid (40 mL) was added to a solution of the resulting pale solid (16.0 g, 52.4 mmol) in dichloromethane (40 mL), and the mixture was  
25 stirred for 2 h at room temperature. Removal of the volatile materials under reduced pressure followed by recrystallization of the residue from ethanol/diethyl ether yielded the trifluoroacetate salt of the desired product **274** (16.4g). <sup>1</sup>H NMR: (DMSO d<sub>6</sub>)  $\delta$  9.35 (br. s, 1H), 8.37 (m, 1H), 7.93 (m, 1H), 7.31 (m, 1H), 7.23 (m, 1H), 3.79 (m, 4H), 3.28 (m, 4H).

Example 164-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-  
piperazine-1-carboxamide 276

5 In accordance with the general Scheme 2A, the following is the preparation of a compound of Structure 5A, wherein each of R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> is hydrogen, m = 2, n = 1; Z is N; Y is N-pyridin-2-yl-carboxamide; and R<sup>1</sup> is naphthyl.

A 0.125 M solution of 4-ethoxymethylene-2-naphthalen-1-yl-4H-oxazol-5-  
10 one in DMSO (200 µL, 25 µmole) was added to a 0.125 M solution of N-pyridin-2-yl-piperazine-1-carboxamide (200 µL, 25 µmole). The reaction vessel was sealed and the resulting mixture shaken at 40° C for 2 h to yield the desired product as a DMSO solution **276** (MH<sup>+</sup> 427).

Similarly, substituting 4-ethoxymethylene-2-naphthalen-1-yl-4H-oxazol-5-  
15 one with other oxazolones, following the procedure described in Example 16, the following compounds were prepared:

4-[2-(4-Fluoro-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamide **278** (MH<sup>+</sup> 445);

4-(5-Oxo-2-quinolin-4-yl-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-  
20 piperazine-1-carboxamide **280** (MH<sup>+</sup> 428);

4-[2-(3-Methoxy-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamide **282** (MH<sup>+</sup> 407);

4-[2-(2,3-Dichloro-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamide **284** (MH<sup>+</sup> 446);

25 4-[2-(2,3-Dimethyl-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamide **286** (MH<sup>+</sup> 405);

4-[5-Oxo-2-(1-phenyl-cyclopentyl)-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamide **288** (MH<sup>+</sup> 445);

4-(5-Oxo-2-m-tolyl-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-piperazine-1-  
30 carboxamide **290** (MH<sup>+</sup> 391);

4-(5-Oxo-2-o-tolyl-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-piperazine-1-carboxamide **292** (MH<sup>+</sup> 391);

4-[2-(1-Methyl-1H-indol-2-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamide **294** (MH<sup>+</sup> 430);

4-[5-Oxo-2-(3-trifluoromethyl-phenyl)-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamide **296** (MH<sup>+</sup> 445);

5 4-(2-Benzo[b]thiophen-2-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-piperazine-1-carboxamide **298** (MH<sup>+</sup> 433);

4-(2-Benzofuran-2-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-piperazine-1-carboxamide **300** (MH<sup>+</sup> 418);

10 4-[2-(2-Chloro-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamide **302** (MH<sup>+</sup> 411);

4-[2-(4-Chloro-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamide **304** (MH<sup>+</sup> 411);

4-[5-Oxo-2-(1-phenyl-cyclopropyl)-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamide **306** (MH<sup>+</sup> 417);

15 4-[2-(3,4-Dimethoxy-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamide **308** (MH<sup>+</sup> 437);

4-[2-(6-Methoxy-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamide **310** (MH<sup>+</sup> 457);

20 4-(2-Naphthalen-2-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-piperazine-1-carboxamide **312** (MH<sup>+</sup> 427);

4-(5-Oxo-2-phenyl-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-piperazine-1-carboxamide **314** (MH<sup>+</sup> 377); and

4-[5-Oxo-2-(2-trifluoromethyl-phenyl)-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamide **316** (MH<sup>+</sup> 445).

25

#### Example 17

4-(2-Benzofuran-7-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-piperazine-1-carboxamide hydrochloride **318**

30

In accordance with the general Scheme 2A, the following is the preparation of a compound of Structure 5A, wherein each of R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> is

- 78 -

hydrogen,  $m = 2$ ,  $n = 1$ ; Z is N; Y is N-pyridin-2-yl-carboxamidine; and  $R^1$  is 2-benzofuran-7-yl.

N,N-diisopropylethylamine (268 mg, 2.07 mmol) was added to a suspension of **274** (300 mg, 0.69 mmol), prepared as described in Example 15, and 2-benzofuran-7-yl-4-ethoxymethylene-4H-oxazol-5-one (178 mg, 0.69 mmol) in acetonitrile (10 mL), and the mixture stirred at room temperature for 1 h. The volatile materials were removed under reduced pressure and the residue recrystallized from ethanol/diethyl ether saturated with gaseous HCl to yield the desired product as its hydrochloride salt **318** (235 mg).  $MH^+$  417;  $^1H$  NMR: (DMSO  $d_6$ )  $\delta$  8.37 (m, 1H), 8.14 (m, 1H), 7.93 (m, 1H), 7.85 (m, 2H), 7.53 (m, 2H), 7.39 (m, 1H), 7.25 (m, 1H), 7.10 (m, 1H), 4.58 (m, 2H), 4.11 (br. s, 2H), 3.88 (m, 6H).

Similarly, substituting 2-benzofuran-7-yl-4-ethoxymethylene-4H-oxazol-5-one with other oxazolones and following the procedure described in Example 17, the following compounds were prepared:

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-piperazine-1-carboxamidine hydrochloride **276**;  $MH^+$  427;  $^1H$  NMR: ( $CD_3OD$ )  $\delta$  9.20 (d, 1H), 8.32 (d, 1H), 8.08 (d, 1H), 7.90 (m, 3H), 7.50 (m, 3H), 7.40 (s, 1H), 7.20 (m, 2H), 4.65 (m, 2H), 3.90 (m, 6H);

4-[2-(4-Fluoro-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamidine hydrochloride **278**; MS: 445;  $^1H$  NMR: ( $CD_3OD$ )  $\delta$  9.18 (d, 1H), 8.40 (d, 1H), 8.20 (m, 2H), 7.90 (m, 1H), 7.70 (m, 2H), 7.45 (s, 1H), 7.30 (m, 3H), 4.70 (m, 2H), 3.95 (m, 6H);

4-[2-(7-Fluoro-benzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamidine hydrochloride **324**;  $MH^+$  435;  $^1H$  NMR (DMSO  $d_6$ )  $\delta$  8.57 (br. s, 1H; exch.  $D_2O$ ), 8.29 (d, 1H), 8.13 (m, 1H), 7.71 (m, 1H), 7.50 (m, 3H), 7.37 (m, 1H), 6.76 (m, 2H), 4.44 (m, 2H), 3.80 (m, 2H), 3.75 (m, 4H);

4-(2-Benzofuran-4-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-piperazine-1-carboxamidine hydrochloride **326**;  $MH^+$  417;  $^1H$  NMR (DMSO  $d_6$ )  $\delta$  10.87 (s, 1H, exch.  $D_2O$ ), 8.37 (d, 1H), 8.20 (d, 1H), 7.93 (m, 1H), 7.75 (m, 2H), 7.59 (m, 1H), 7.55 (s, 1H), 7.43 (m, 2H), 7.25 (m, 1H), 4.58 (m, 2H), 3.90 (m, 6H);

4-[2-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamidine hydrochloride **328** ( $MH^+$  435); and

4-[2-(2,3-Dihydro-benzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamidine hydrochloride **330** ( $MH^+$  419).

5

### Example 18

#### N-Phenyl-piperazine-1-carboxamidine trifluoroacetate **332**

In accordance with the general Scheme 2A, the following is the  
10 preparation of a compound of Structure 4A, wherein each of  $R^{2a}$ ,  $R^{2b}$  and  $R^{2c}$  is hydrogen,  $m = 2$ ,  $n = 1$ ; Z is N; and Y is N-phenyl-carboxamidine.

Methyl iodide (301 g, 2.12 mol) was added dropwise, over 30 min, to a solution of phenyl thiourea (300 g, 1.93 mol) in ethanol (1.5 L). The resulting solution was refluxed for 1 hour and cooled to room temperature. Concentration  
15 of the solution to approximately half its volume yielded a white precipitate that was collected by filtration, washed on the filter with diethyl ether and dried to yield a white solid (532 g). The resulting white solid (200 g, 0.68 mol) was dissolved in 4 M aqueous sodium hydroxide (1 L) and the resulting solution extracted with chloroform (4 x 400 mL). The combined chloroform extracts were  
20 dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure yielding a thick oil (92.7 g).

N-*tert*-butoxycarbonyl-piperazine (100 g, 0.54 mol) was added to a solution of the thick oil (89.1 g, 0.54 mol) in isopropanol (1 L), and the mixture refluxed overnight. The mixture was cooled to room temperature and the volatile  
25 materials removed under reduced pressure. Recrystallization of the residue from ethanol/H<sub>2</sub>O yielded a white solid (82.0 g).

A solution of the white solid (25.7 g) in dichloromethane (125 mL) was cooled to 0° C and trifluoroacetic acid (125 mL) added dropwise over 30 min. The ice bath was removed and the mixture was warmed up to room temperature  
30 and stirred for 1 h. Removal of the volatile materials under reduced pressure followed by recrystallization from ethanol/diethyl ether yielded the desired product as its trifluoroacetate salt **332**. <sup>1</sup>H NMR: (DMSO d<sub>6</sub>)  $\delta$  9.08 (br. s, 1H,

exch. D<sub>2</sub>O), 8.22 (br. s, 1H, exch. D<sub>2</sub>O), 7.53 (m, 2H), 7.34 (m, 3H), 3.78 (m, 4H), 3.36 (m, 4H).

### Example 19

5

#### 4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl- piperazine-1-carboxamide 334

In accordance with the general Scheme 2A, the following is the preparation of a compound of Structure 5A, wherein each of R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> is  
10 hydrogen, m = 2, n = 1; Z is N; Y is N-phenyl-carboxamidine; and R<sup>1</sup> is naphthyl.

To a 0.25 M solution of N-phenyl-piperazine-1-carboxamidine (200 µL, 50 µmole) was added a 0.25 M solution of 4-ethoxymethylene-2-naphthalen-1-yl-4H-oxazol-5-one in DMSO (200 µL, 25 µmole). The reaction vessel was sealed and the resulting mixture shaken at room temperature for 1 h to yield the desired  
15 product as a DMSO solution **334** (MH<sup>+</sup> 426).

Similarly, substituting 4-ethoxymethylene-2-naphthalen-1-yl-4H-oxazol-5-one with other oxazolones and following the procedure described in Example 19, the following compounds were prepared:

4-[2-(4-Fluoro-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-  
20 piperazine-1-carboxamidine **336** (MH<sup>+</sup> 444);

4-(2-Benzofuran-4-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamidine **338** (MH<sup>+</sup> 416);

4-[2-(3-Methoxy-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-piperazine-1-carboxamidine **340** (MH<sup>+</sup> 406);

25 4-(5-Oxo-2-m-tolyl-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamidine **342** (MH<sup>+</sup> 390);

4-[2-(2,3-Dimethyl-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-piperazine-1-carboxamidine **344** (MH<sup>+</sup> 404);

30 4-(5-Oxo-2-quinolin-4-yl-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamidine **346** (MH<sup>+</sup> 427);

4-(2-Benzo[b]thiophen-2-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamidine **348** (MH<sup>+</sup> 432);

4-[2-(2,3-Dichloro-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-  
piperazine-1-carboxamidine **350** ( $MH^+$  446);

4-[2-(3,4-Dimethoxy-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-  
piperazine-1-carboxamidine **352** ( $MH^+$  436);

5        4-[2-(1-Methyl-1H-indol-2-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-  
piperazine-1-carboxamidine **354** ( $MH^+$  429);

4-[2-(1H-Indol-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-piperazine-1-  
carboxamidine **356** ( $MH^+$  416);

4-[5-Oxo-2-(2-trifluoromethyl-phenyl)-oxazol-4-ylidenemethyl]-N-phenyl-  
10 piperazine-1-carboxamidine **358** ( $MH^+$  444);

4-(2-Naphthalen-2-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-  
1-carboxamidine **360** ( $MH^+$  426);

4-[2-(2,4-Dichloro-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-  
piperazine-1-carboxamidine **362** ( $MH^+$  445);

15        4-[2-(6-Methoxy-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-  
phenyl-piperazine-1-carboxamidine **364** ( $MH^+$  456);

4-(5-Oxo-2-o-tolyl-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-  
carboxamidine **366** ( $MH^+$  390);

4-[5-Oxo-2-(3,4,5-trimethoxy-phenyl)-oxazol-4-ylidenemethyl]-N-phenyl-  
20 piperazine-1-carboxamidine **368** ( $MH^+$  467);

4-[2-(3-Methoxy-naphthalen-2-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-  
phenyl-piperazine-1-carboxamidine **370** ( $MH^+$  456);

4-[2-(4-Chloro-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-  
piperazine-1-carboxamidine **372** ( $MH^+$  411); and

25        4-[2-(5-Fluoro-2-methyl-phenyl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-  
piperazine-1-carboxamidine **374** ( $MH^+$  408).



Example 204-(2-Benzofuran-7-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-  
piperazine-1-carboxamidine hydrochloride 376

5 In accordance with the general Scheme 2A, the following is the preparation of a compound of Structure 5A, wherein each of R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> is hydrogen, m = 2, n = 1; Z is N; Y is N-phenyl-carboxamidine; and R<sup>1</sup> is 2-benzofuran-7-yl.

To a suspension of **332** (672 mg, 1.55 mmol) prepared as described in  
10 Example 18, and 2-benzofuran-7-yl-4-ethoxymethylene-4H-oxazol-5-one (400 mg, 1.55 mmol) in acetonitrile (15 mL) was added N,N-diisopropylethylamine (1.0 g, 7.77 mmol) and the mixture stirred at room temperature for 1 h. The volatile materials were removed under reduced pressure and the residue recrystallized from ethanol/diethyl ether saturated with gaseous HCl to yield the desired  
15 product as its hydrochloride salt **376** (202 mg). M<sup>+</sup> 415, <sup>1</sup>H NMR: (DMSO d<sub>6</sub>) δ 8.17 (br. s, 1H, exch. D<sub>2</sub>O), 8.11 (m, 1H), 7.82 (m, 2H), 7.53 (s, 1H), 7.48-7.36 (m, 3H), 7.29-7.23 (m, 3H), 7.09 (m, 1H), 4.57 (m, 2H), 3.87 (m, 2H), 3.77 (m, 4H).

Similarly, substituting **332** with other substituted amines, and 2-  
20 benzofuran-7-yl-4-ethoxymethylene-4H-oxazol-5-one with other oxazolones, following the procedure described in Example 20, the following compounds were prepared:

4-[2-(4-Fluoro-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-  
piperazine-1-carboxamidine hydrochloride **336**; MH<sup>+</sup> 444; <sup>1</sup>H NMR: (DMSOd<sub>6</sub>) δ  
25 9.90 (s, 1H), 9.30 (d, 1H), 8.15 (m, 4H), 7.80 (m, 2H), 7.55 (s, 1H), 7.50 (m, 3H), 7.30 (m, 2H), 4.75 (m, 2H), 3.90 (m, 2H), 3.80 (m, 2H), 3.75 (m, 2H);

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-  
1-carboxamidine hydrochloride **334**; MH<sup>+</sup> 426; <sup>1</sup>H NMR: (CD<sub>3</sub>OD) δ 9.25 (d, 1H),  
8.15 (d, 1H), 8.05 (d, 1H), 7.95 (d, 1H), 7.50 (m, 6H), 7.35 (m, 3H), 4.70 (m, 2H),  
30 3.95 (m, 6H);

4-[2-(7-Fluoro-benzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-  
piperazine-1-carboxamidine hydrochloride **382**; MH<sup>+</sup> 434; <sup>1</sup>H NMR (DMSO d<sub>6</sub>) δ

9.78 (s, 1H), 8.19 (d, 1H), 7.16 (m, 1H), 7.43 (s, 1H), 7.39-7.14 (m, 7H), 4.43 (m, 2H), 3.77 (m, 2H), 3.72 (m, 2H), 3.64 (m, 2H);

4-(2-Benzofuran-4-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamide hydrochloride **338**;  $MH^+$  416;  $^1H$  NMR (DMSO  $d_6$ )  $\delta$  8.24 (br. s, 1H, exch.  $D_2O$ ), 8.16 (d, 1H), 7.75 (m, 2H), 7.56 (s, 1H), 7.44 (m, 4H), 7.27 (m, 3H), 4.57 (m, 2H), 3.88 (m, 4H), 3.81 (m, 2H);

4-[2-(2,3-Dihydro-benzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-piperazine-1-carboxamide hydrochloride **386** ( $MH^+$  418);

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-thiophen-2-yl-piperazine-1-carboxamide hydrochloride **388** ( $MH^+$  432);

4-[2-(4-Fluoro-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-thiophen-2-yl-piperazine-1-carboxamide hydrochloride **390** ( $M^+$  449);

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-o-tolyl-piperazine-1-carboxamide hydrochloride **392** ( $M^+$  439);

N-(3-Cyano-phenyl)-4-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxamide hydrochloride **394** ( $MH^+$  451);

N-(3-Methoxy-phenyl)-4-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxamide hydrochloride **396** ( $M^+$  455);

N-(2-Chloro-phenyl)-4-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxamide hydrochloride **398** ( $MH^+$  460);

N-(4-Benzyloxy-phenyl)-4-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxamide hydrochloride **400** ( $MH^+$  532); and

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N,N-diphenyl-piperazine-1-carboxamide hydrochloride **402** ( $MH^+$  502).

### Example 21

#### N-(4-Chloro-phenyl)-4-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxamide hydrochloride **404**

In accordance with the general Scheme 3A, the following is the preparation of a compound of Structure 5A, wherein each of  $R^{2a}$ ,  $R^{2b}$  and  $R^{2c}$  is

hydrogen,  $m = 2$ ,  $n = 1$ ; Z is N; Y is N-(4-chloro-phenyl)-carboxamidine; and  $R^1$  is naphthyl.

Triethylamine (154 mg, 1.52 mmol) was added to a suspension of 1-(4-chloro-phenyl)-2-methyl-isothiourea hydroiodide (200 mg, 0.6 mmol) and **50** (187 mg, 0.6 mmol), as produced in Example 3, in DMF (5 mL). The mixture was heated at reflux for 30 min, cooled to room temperature and the insoluble precipitate removed. The DMF solution was evaporated under reduced pressure and the residue purified by flash chromatography over silica gel (eluent dichloromethane:methanol:  $NH_4OH$ , 93:7:0.1) to yield a yellow oil. Further purification by preparative thin layer chromatography yielded the desired product as a yellow powder. Recrystallization from ethanol/diethyl ether saturated with gaseous HCl yielded the hydrochloride salt **404**.  $MH^+$  460;  $^1H$  NMR: (DMSO  $d_6$ )  $\delta$  10.22 (s, 1H), 9.20 (d, 1H), 8.22 (br. s, 2H, exch.  $D_2O$ ), 8.12-8.03 (m, 3H), 7.69-7.59 (m, 3H), 7.57 (s, 1H), 7.50 (d, 2H), 7.31 (d, 2H), 4.56 (m, 2H), 3.88 (m, 4H), 3.79 (m, 2H).

Similarly, substituting 1-(4-Chloro-phenyl)-2-methyl-isothiourea with other 2-methyl-isothiourea derivatives and following the procedure described in Example 21, the following compounds were prepared:

N-(4-Cyclohexyl-phenyl)-4-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxamidine hydrochloride **406** ( $MH^+$  508);  
4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-m-tolyl-piperazine-1-carboxamidine hydrochloride **408** ( $MH^+$  440); and  
N-(2-Isopropyl-phenyl)-4-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxamidine hydrochloride **410** ( $MH^+$  468).

## Example 22

### 2-Piperazin-1-yl-1H-benzoimidazole trifluoroacetate **412**

In accordance with the general Scheme 2A, the following is the preparation of a compound of Structure 4A, wherein each of  $R^{2a}$ ,  $R^{2b}$  and  $R^{2c}$  is hydrogen,  $m = 2$ ,  $n = 1$ ; Z is N; and Y is benzoimidazolyl.

A mixture of 2-chlorobenzimidazole (3.05 g, 20 mmol) and N-*tert*-butoxycarbonyl-piperazine (3.65 g, 19.6 mmol) in 1-butanol (40 mL) was refluxed for 6 h and cooled to room temperature. The resulting white precipitate (5.02 g) was collected by filtration and dried.

5 Trifluoroacetic acid (10 mL) was added to a solution of the white precipitate in dichloromethane (20 mL). The mixture was stirred at room temperature for 2 h and evaporated under reduced pressure. The residue was triturated with *tert*-butyl methyl ether and the resulting white precipitate collected by filtration to yield the desired product as its trifluoroacetate salt **412**.  $\text{MH}^+$  203,  
10  $^1\text{H}$  NMR: ( $\text{D}_2\text{O}$ )  $\delta$  7.48 (m, 2H), 7.38 (m, 2H), 3.98 (m, 4H), 3.55 (m, 4H).

### Example 23

#### 2-(Hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-1H-benzimidazole hydrochloride **414**

15 In accordance with the general Scheme 2C, the following is the preparation of a compound of Structure 4C, wherein each of p, q, r and s = 1; and Y is benzoimidazolyl.

To a solution of **198** (3.0 g, 15 mmol), prepared as described in Example 9, in 1-butanol (30 mL), 2-chlorobenzimidazole (2.26 g, 15 mmol) was added,  
20 and the resulting solution was refluxed overnight under a nitrogen atmosphere. On cooling to room temperature the solution was evaporated under reduced pressure. The residue was dissolved in chloroform (100 mL), and washed with water (2 x 20 mL) and brine (2 x 20 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure  
25 to yield a colorless foam (2.17 g).

To a solution the colorless foam (2.17 g, 6.8 mmol) in ethanol (100 mL), ammonium formate (4.29 g, 68.1 mmol) was added, followed by 10% palladium on carbon (1.0 g). The resulting mixture was refluxed for 3 h, cooled to room temperature, filtered through Celite and evaporated under reduced pressure to  
30 yield a white powder. Recrystallization of this powder from ethanol/diethyl ether saturated with gaseous HCl yielded the hydrochloride salt of the desired product

**414** (1.32 g).  $^1\text{H}$  NMR: (DMSO  $d_6$ )  $\delta$  13.37 (br. s, 1H, exch.  $\text{D}_2\text{O}$ ), 7.42 (m, 2H), 7.26 (m, 2H), 3.87-3.72 (m, 4H), 3.42-3.18 (m, 6H).

#### Example 24

5

#### 4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]- 2-naphthalen-1-yl-4H-oxazol-5-one **416**

In accordance with the general Scheme 2A, the following is the preparation of a compound of Structure 5A, wherein each of  $\text{R}^{2a}$ ,  $\text{R}^{2b}$  and  $\text{R}^{2c}$  is hydrogen,  $m = 2$ ,  $n = 1$ ; Z is N; Y is benzoimidazol-2-yl; and  $\text{R}^1$  is naphthyl.

A 0.25 M solution of 4-ethoxymethylene-2-naphthalen-1-yl-4H-oxazol-5-one in DMSO (200  $\mu\text{L}$ , 25  $\mu\text{mole}$ ) was added to a 0.25 M solution of 2-piperazin-1-yl-1H-benzoimidazole (200  $\mu\text{L}$ , 50  $\mu\text{mole}$ ). The reaction vessel was sealed and the resulting mixture shaken at room temperature for 1 h to yield the desired product as a DMSO solution **416** ( $\text{MH}^+$  424).

Similarly, substituting 4-ethoxymethylene-2-naphthalen-1-yl-4H-oxazol-5-one with other oxazolones, following the procedure described in Example 24, the following compounds were prepared:

4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(4-fluoro-  
naphthalen-1-yl)-4H-oxazol-5-one **418** ( $\text{MH}^+$  442);

4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(2,3-dichloro-phenyl)-4H-oxazol-5-one **420** ( $\text{MH}^+$  442);

4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(3-methoxy-phenyl)-4H-oxazol-5-one **422** ( $\text{MH}^+$  404);

4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-m-tolyl-4H-oxazol-5-one **424** ( $\text{MH}^+$  388);

4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(2,3-dimethyl-phenyl)-4H-oxazol-5-one **426** ( $\text{MH}^+$  402);

4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(2-trifluoromethyl-phenyl)-4H-oxazol-5-one **428** ( $\text{MH}^+$  443);

4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(2,3-difluoro-phenyl)-4H-oxazol-5-one **430** ( $\text{MH}^+$  409);

- 4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-o-tolyl-4H-oxazol-5-one **432** ( $MH^+$  388);
- 4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(2-chlorophenyl)-4H-oxazol-5-one **434** ( $MH^+$  408);
- 5 4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(3,4-dimethoxyphenyl)-4H-oxazol-5-one **436** ( $MH^+$  434);
- 4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-phenyl-4H-oxazol-5-one **438** ( $MH^+$  374);
- 4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(3-trifluoromethyl-phenyl)-4H-oxazol-5-one **440** ( $MH^+$  441);
- 10 4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(3-methoxynaphthalen-2-yl)-4H-oxazol-5-one **442** ( $MH^+$  454);
- 4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-thiophen-2-yl-4H-oxazol-5-one **444** ( $MH^+$  380);
- 15 2-Benzo[1,3]dioxol-5-yl-4-[4-(1H-benzoimidazol-2-yl)-piperazin-1-ylmethylene]-4H-oxazol-5-one **446** ( $MH^+$  417);
- 4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-naphthalen-2-yl-4H-oxazol-5-one **448** ( $MH^+$  424);
- 4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(4-chlorophenyl)-4H-oxazol-5-one **450** ( $MH^+$  408);
- 20 4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(6-methoxynaphthalen-1-yl)-4H-oxazol-5-one **452** ( $MH^+$  454);
- 2-Benzo[b]thiophen-2-yl-4-[4-(1H-benzoimidazol-2-yl)-piperazin-1-ylmethylene]-4H-oxazol-5-one **454** ( $MH^+$  430); and
- 25 4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-quinolin-3-yl-4H-oxazol-5-one **456** ( $MH^+$  424).

Example 252-Benzofuran-4-yl-4-[4-(1H-benzoimidazol-2-yl)-piperazin-1-ylmethylene]-  
4H-oxazol-5-one 458

5 In accordance with the general Scheme 2A, the following is the preparation of a compound of Structure 5A, wherein each of R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> is hydrogen, m = 2, n = 1; Z is N; Y is benzoimidazol-2-yl; and R<sup>1</sup> is 2-benzofuran-7-yl.

N,N-Diisopropylethylamine (403 mg, 3.1 mmol) was added to a  
10 suspension of **412** (246 mg, 0.78 mmol), prepared as described in Example 22, and 2-benzofuran-4-yl-4-ethoxymethylene-4H-oxazol-5-one (200 mg, 0.78 mmol) in acetonitrile (10 mL). The resulting mixture was stirred overnight at room temperature. The resulting yellow precipitate was filtered, washed with acetonitrile and dried under vacuum to yield the desired product **458** (186 mg).  
15 M<sup>+</sup> 413, <sup>1</sup>H NMR: (DMSO d<sub>6</sub>) δ 8.20 (d, 1H), 7.77 (m, 2H), 7.53 (s, 1H), 7.45 (m, 2H), 7.25 (m, 2H), 6.97 (m, 2H), 4.57 (m, 2H), 3.84 (m, 4H), 3.72 (m, 2H).

Similarly, substituting 2-piperazin-1-yl-1H-benzoimidazole with other substituted amines, and 2-benzofuran-4-yl-4-ethoxymethylene-4H-oxazol-5-one with other oxazolones, following the procedure described in Example 25, the  
20 following compounds were prepared:

4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(4-fluoronaphthalen-1-yl)-4H-oxazol-5-one **418**; MH<sup>+</sup> 442; <sup>1</sup>H NMR: (CD<sub>3</sub>OD) δ 9.25 (d, 1H), 8.15 (m, 2H), 7.66 (m, 2H), 7.60 (m, 6H), 4.70 (m, 2H), 3.90 (m, 6H);

4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-naphthalen-1-yl-  
25 4H-oxazol-5-one **416**; MH<sup>+</sup> 424; <sup>1</sup>H NMR (DMSO d<sub>6</sub>) δ 9.24 (d, 1H), 8.11 (m, 3H), 7.72-7.59 (m, 4H), 7.45 (m, 2H), 7.27 (m, 2H), 4.65 (m, 2H), 4.04 (m, 2H), 3.97 (m, 4H);

4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(7-fluorobenzofuran-4-yl)-4H-oxazol-5-one **464**; MH<sup>+</sup> 432; <sup>1</sup>H NMR: (DMSO d<sub>6</sub>) δ 8.30 (d,  
30 1H), 7.73 (m, 1H), 7.53 (s, 1H), 7.51 (m, 1H), 7.37 (m, 1H), 7.23 (m, 2H), 6.95 (m, 2H), 4.54 (m, 2H), 3.84 (m, 4H), 3.72 (m, 2H);

4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-4H-oxazol-5-one **466** ( $MH^+$  432);

4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(2,3-dihydro-benzofuran-4-yl)-4H-oxazol-5-one **468** ( $M^+$  415);

5 2-Benzo[1,3]dioxol-4-yl-4-[4-(1H-benzoimidazol-2-yl)-piperazin-1-ylmethylene]-4H-oxazol-5-one **470** ( $MH^+$  418);

4-[4-(6-Methoxy-1H-benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-naphthalen-1-yl-4H-oxazol-5-one **472** ( $MH^+$  454);

10 2-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-4-[4-(6-methoxy-1H-benzoimidazol-2-yl)-piperazin-1-ylmethylene]-4H-oxazol-5-one **474** ( $MH^+$  462);

4-(4-Benzooxazol-2-yl-piperazin-1-ylmethylene)-2-naphthalen-1-yl-4H-oxazol-5-one **476** ( $MH^+$  425);

4-(4-Benzothiazol-2-yl-piperazin-1-ylmethylene)-2-naphthalen-1-yl-4H-oxazol-5-one **478** ( $MH^+$  441);

15 4-[4-(1H-Benzoimidazol-2-ylmethyl)-piperazin-1-ylmethylene]-2-naphthalen-1-yl-4H-oxazol-5-one **480** ( $MH^+$  438); and

2-Benzofuran-4-yl-4-[5-(1H-benzoimidazol-2-yl)-hexahydro-pyrrolo[3,4-c]pyrrol-2-ylmethylene]-4H-oxazol-5-one **482** ( $M^+$  439).

20

#### Example 26

#### 4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]- 2-naphthalen-1-yl-4H-oxazol-5-one **416**

25 In accordance with the general Scheme 3A, the following is the preparation of a compound of Structure 5A, wherein each of  $R^{2a}$ ,  $R^{2b}$  and  $R^{2c}$  is hydrogen,  $m = 2$ ,  $n = 1$ ; Z is N; Y is benzoimidazol-2-yl; and  $R^1$  is naphthyl.

A mixture of 2-chlorobenzoimidazole (218 mg, 1.43 mmol) and (200 mg, 0.65 mmol), as produced in Example 3, in 1-butanol was heated to 100° C overnight. The resulting yellow precipitate was filtered and washed with hot 1-butanol to yield the desired product **416** (240 mg).  $MH^+$  424;  $^1H$  NMR (DMSO  $d_6$ )  $\delta$  9.22 (d, 1H), 8.10 (m, 4H), 7.65 (m, 5H), 7.50 (m, 3H), 7.30 (m, 2H), 7.40 (m, 2H), 4.65 (m, 2H), 4.00 (m, 6H).

30



Similarly, substituting 2-chlorobenzoimidazole with other substituted imidazoles and following the procedure described in Example 26, the following examples were prepared:

- 4-[4-(3H-Imidazo[4,5-b]pyridin-2-yl)-piperazin-1-ylmethylene]-2-naphthalen-1-yl-4H-oxazol-5-one hydrochloride **486** ( $M^+$  425);
- 4-[4-(3H-Imidazo[4,5-c]pyridin-2-yl)-piperazin-1-ylmethylene]-2-naphthalen-1-yl-4H-oxazol-5-one hydrochloride **488** ( $M^+$  425); and
- 4-[4-(5-Chloro-1H-benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-naphthalen-1-yl-4H-oxazol-5-one hydrochloride **490** ( $M^+$  458).

#### Example 27

##### 4-[4-(1-Methyl-1H-benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-naphthalen-1-yl-4H-oxazol-5-one **492**

In accordance with the general Scheme 3A, the following is the preparation of a compound of Structure 5A, wherein each of  $R^{2a}$ ,  $R^{2b}$  and  $R^{2c}$  is hydrogen,  $m = 2$ ,  $n = 1$ ; Z is N; Y is 1-methyl-benzoimidazol-2-yl; and  $R^1$  is naphthyl.

To a solution of **416** (43 mg, 0.1 mmol) prepared as described in Example 26, in DMF (1 mL) sodium carbonate (10 mg, 0.1 mmol) was added, followed by iodomethane (62 mL, 0.1 mmol). The resulting mixture was stirred at 70° C for 24 h, cooled to room temperature and the volatile materials were removed under reduced pressure to yield a yellow solid. The yellow solid was partitioned between chloroform and water, the organic phase separated, dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to yield an orange residue. Recrystallization of the orange residue from methanol yielded yellow crystals of the desired product **492** (15 mg).  $MH^+$  438;  $^1H$  NMR: (DMSO  $d_6$ )  $\delta$  9.19 (d, 1H), 8.08 (m, 3H), 7.63 (m, 3H), 7.57 (s, 1H), 7.38 (m, 2H), 7.12 (m, 2H), 4.64 (m, 2H), 3.93 (m, 2H), 3.68 (s, 3H), 3.47 (m, 4H).

Example 281-(4,5-Dihydro-1H-imidazol-2-yl)-piperazine trifluoroacetate 494

In accordance with the general Scheme 2A, the following is the  
5 preparation of a compound of Structure 4A, wherein each of  $R^{2a}$ ,  $R^{2b}$  and  $R^{2c}$  is hydrogen,  $m = 2$ ,  $n = 1$ ; Z is N; and Y is 4,5-dihydro-1H-imidazol-2-yl.

2-Chloro-4,5-dihydro-1H-imidazole sulfate (10.0 g, 49.3 mmol) was  
partitioned between saturated aqueous  $\text{NaHCO}_3$  (200 mL) and diethyl ether (200  
mL). The organic phase was separated and the aqueous phase further extracted  
10 with diethyl ether (2 x 100 mL). The combined diethyl ether extract was dried  
over anhydrous magnesium sulfate and filtered. This ether solution was added  
to a solution of N-*tert*-butoxycarbonyl-piperazine (9.20 g, 49.3 mmol) in  
isopropanol (200 mL). The diethyl ether was evaporated from the combined  
solutions using a rotavapor to yield a residue. The resulting residue was heated  
15 at reflux for 90 min, cooled to room temperature and reduced in volume to  
approximately 50 mL. Crystals precipitated from this solution on standing and  
were collected by filtration, washed on the filter with diethyl ether and dried under  
vacuum to yield the N-*tert*-butoxy carbonyl-protected intermediate (4.2 g).

The crystalline solid intermediate was dissolved in dichloromethane (20  
20 mL). Trifluoroacetic acid (20 mL) was added to the solution and the reaction  
mixture was stirred for 2.5 h at room temperature. The volatile materials were  
removed under reduced pressure to yield a colorless oil that slowly crystallized  
on standing. Triturating with diethyl ether yielded the desired product (3.93 g) as  
its trifluoroacetate salt **494**.  $\text{MH}^+$  256;  $^1\text{H}$  NMR: (DMSO  $d_6$ )  $\delta$  8.74 (br. s, 1H,  
25 exch.  $\text{D}_2\text{O}$ ), 3.64 (m, 4H), 3.35 (s, 4H), 3.23 (m, 4H).

Example 291-(4,5-Dihydro-oxazol-2-yl)-piperazine trifluoroacetate 496

30 In accordance with the general Scheme 2A, the following is the  
preparation of a compound of Structure 4A, wherein each of  $R^{2a}$ ,  $R^{2b}$  and  $R^{2c}$  is  
hydrogen,  $m = 2$ ,  $n = 1$ ; Z is N; and Y is 4,5-dihydro-oxazol-2-yl.

- 92 -

2-Chloroethyl isocyanate (3.4 g, 32.2 mmol) was added to a solution of N-*tert*-butoxycarbonyl-piperazine (5.0 g, 26.8 mmol) in tetrahydrofuran (30 mL) under a nitrogen atmosphere and the mixture was stirred overnight at room temperature. A small amount of solid precipitated into the reaction mixture. The  
5 resulting suspension was poured into vigorously stirring hexane (400 mL), the resulting precipitate collected by filtration and dried under vacuum to yield chloroethyl urea (7.40 g).

Potassium fluoride (40% by weight on alumina, 15.0 g) was added to a solution of (7.40 g, 25.4 mmol) in acetonitrile (160 mL), and the resulting mixture  
10 was refluxed overnight. The reaction mixture was filtered and evaporated under reduced pressure to yield a colorless oil (9.2 g).

Trifluoroacetic acid (35 mL) was added to a solution of the colorless oil in dichloromethane (35 mL) and the mixture stirred at room temperature for 4 h. The volatile materials were removed under vacuum to yield the desired product  
15 as its trifluoroacetate salt **496**. <sup>1</sup>H NMR: (DMSO d<sub>6</sub>) δ 4.67 (m, 2H), 3.73 (m, 2H), 3.57 (m, 2H), 3.31 (m, 2H), 3.11 (m, 2H), 2.91 (m, 2H).

### Example 30

20 2-Benzofuran-7-yl-4-[4-(4,5-dihydro-1H-imidazol-2-yl)-piperazin-1-ylmethylene]-  
4H-oxazol-5-one hydrochloride 498

In accordance with the general Scheme 2A, the following is the preparation of a compound of Structure 5A, wherein each of R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> is hydrogen, m = 2, n = 1; Z is N; Y is 4,5-dihydro-1H-imidazol-2-yl; and R<sup>1</sup> is 2-  
25 benzofuran-7-yl.

N,N-Diisopropylethylamine (383mg, 3 mmol) was added to a suspension of **494** (382 mg, 1mmol), prepared as described in Example 28, and 2-benzofuran-7-yl-4-ethoxymethylene-4H-oxazol-5-one (257 mg, 1 mmol) in acetonitrile (10 mL), and the mixture was stirred at room temperature for 24 h.  
30 The resulting precipitate was collected by filtration and dried under vacuum. Recrystallization of the resulting solid from ethanol/diethyl ether saturated with gaseous HCl yielded the desired product (218 mg) as its hydrochloride salt **498**.

- 93 -

MH<sup>+</sup> 366; <sup>1</sup>H NMR: (DMSO d<sub>6</sub>) δ 9.00 (br. s, 1H, exch. D<sub>2</sub>O), 8.13 (d, 1H), 7.82 (m, 2H), 7.50 (s, 1H), 7.39 (t, 1H), 7.08 (d, 1H), 4.52 (m, 2H), 3.81 (m, 6H), 3.68 (s, 4H).

Similarly, substituting 1-(4,5-Dihydro-1H-imidazol-2-yl)-piperazine with  
5 other substituted amines, and 2-benzofuran-7-yl-4-ethoxymethylene-4H-oxazol-5-one with other oxazolones, following the procedure described in Example 30, the following compounds were prepared:

4-[4-(4,5-Dihydro-1H-imidazol-2-yl)-piperazin-1-ylmethylene]-2-(4-fluoro-naphthalen-1-yl)-4H-oxazol-5-one **500** (MH<sup>+</sup> 394);

10 2-Benzofuran-4-yl-4-[4-(4,5-dihydro-1H-imidazol-2-yl)-piperazin-1-ylmethylene]-4H-oxazol-5-one **502** (MH<sup>+</sup> 366);

2-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-4-[4-(4,5-dihydro-1H-imidazol-2-yl)-piperazin-1-ylmethylene]-4H-oxazol-5-one **504** (MH<sup>+</sup> 384); and

15 4-[4-(4,5-Dihydro-oxazol-2-yl)-piperazin-1-ylmethylene]-2-naphthalen-1-yl-4H-oxazol-5-one **506** (MH<sup>+</sup> 377).

### Example 31

20 4-[4-(4,5-Dihydro-1H-imidazol-2-yl)-piperazin-1-ylmethylene]-2-naphthalen-1-yl-4H-oxazol-5-one **508**

In accordance with the general Scheme 2A, the following is the preparation of a compound of Structure 5A, wherein each of R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> is hydrogen, m = 2, n = 1; Z is N; Y is 4,5-dihydro-1H-imidazol-2-yl; and R<sup>1</sup> is naphthyl.

25 2-Chloro-4,5-dihydro-1H-imidazole sulfate (41 mg, 0.2 mmol) was partitioned between saturated aqueous NaHCO<sub>3</sub> and diethyl ether, the phases separated and the aqueous phase further extracted with diethyl ether. The combined diethyl ether extracts were dried over anhydrous magnesium sulfate, filtered and added to a solution of **50** prepared as described in Example 3 (61  
30 mg, 0.2 mmol) in isopropanol. The diethyl ether was removed from the combined solution by evaporation under reduced pressure and the residue was refluxed for 10 min before cooling to room temperature to yield a yellow solid,

which was collected by filtration and recrystallized from isopropanol yielding the desired product **508** (40 mg).  $MH^+$  376;  $^1H$  NMR: ( $CD_3OD$ )  $\delta$  9.1 (d, 2H), 7.95-7.70 (m, 3H), 7.40 (m, 3H), 7.22 (s, 1H), 4.45 (m, 2H), 3.60 (m 10H).

5

### Example 32

#### 4-[2-(4-Fluoro-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxamide hydrochloride **510**

In accordance with the general Scheme 2A, the following is the  
10 preparation of a compound of Structure 5A, wherein each of  $R^{2a}$ ,  $R^{2b}$  and  $R^{2c}$  is hydrogen,  $m = 2$ ,  $n = 1$ ; Z is N; Y is carboxamide; and  $R^1$  is 4-fluoro-1-naphthyl.

A solution of 4-ethoxymethylene-2-(4-fluoro-naphthalen-1-yl)-4H-oxazol-5-one (178 mg, 0.5 mmole) in tetrahydrofuran (5 mL) was added to a mixture of piperazine-1-carboxamide (143 mg, 0.5 mmol) and triethylamine (210  $\mu$ L) in  
15 tetrahydrofuran (10 mL) at 0° C. After 20 min, the solvents were removed and the residue dried. The residue was redissolved in tetrahydrofuran (5 mL) and treated with 4 M hydrochloric acid in dioxane (2 mL) at 0°C. A yellow precipitate was formed which was filtered, washed with tetrahydrofuran and dried under vacuum to afford the desired product **510** (125 mg).  $MH^+$  368.

20 Similarly, substituting 4-ethoxymethylene-2-(4-fluoro-naphthalen-1-yl)-4H-oxazol-5-one with other oxazolones and following the procedure described in Example 32, the following compound was prepared:

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxamide hydrochloride **512** ( $MH^+$  351).

25

### Example 33

#### N-Pyridin-4-yl-piperazine-1-carboxamide trifluoroacetate **514**

In accordance with the general Scheme 2A, the following is the  
30 preparation of a compound of Structure 4A, wherein each of  $R^{2a}$ ,  $R^{2b}$  and  $R^{2c}$  is hydrogen,  $m = 2$ ,  $n = 1$ ; Z is N; and Y is N-pyridin-4-yl-carboxamide.

1,1-Thiocarbonyldiimidazole (29.4 g, 0.16 mol) was added to a solution of 4-aminopyridine (14.1 g, 0.15 mol) in anhydrous tetrahydrofuran (600 mL) and the resulting mixture stirred for 17 h. The solvent was removed under reduced pressure and the resulting solid suspended in a mixture of dichloromethane and water. Filtration of the undissolved solid followed by washing with acetone yielded a solid product (8.98 g).

Gaseous ammonia was bubbled through a solution of the resulting solid product (8.50 g, 0.06 mol) in anhydrous tetrahydrofuran (250 mL) for 20 min. The ammonia flow was discontinued and the mixture was stirred for 17 h during which time a precipitate was formed in the reaction. Filtration followed by drying the solid under vacuum yielded the desired thiourea product (5.1 g).

A mixture of the thiourea product (3.90 g, 26 mmol), *N-tert*-butoxycarbonyl-piperazine (4.84 g, 26 mmol) and 1,3-dicyclohexylcarbodiimide (5.90 g, 28 mmol) in dioxane (105 mL) was refluxed under a nitrogen for 48 h. The solvent was removed under reduced pressure and the residue sonicated in toluene and filtered. The residue was concentrated to approximately one third its volume and filtered to yield the *N-tert*-butoxycarbonyl-protected intermediate (660 mg). Trifluoroacetic acid (12.8 mL) was added to a suspension of the protected intermediate (656 mg) in dichloromethane (12.8 mL) and the resulting solution was stirred for 1 h. Removal of the volatile materials under reduced pressure followed by trituration with diethyl ether yielded the crystalline product (1.68 g) as its trifluoroacetate salt **514**.  $MH^+$  206;  $^1H$  NMR (DMSO  $d_6$ )  $\delta$  9.2 (br. s, 1H), 8.75 (br. s, 1H), 8.5 (m, 1H), 7.32 (m, 1H), 3.75 (m, 4H), 3.40 (m, 4H).

#### Example 34

#### 4-[2-(4-Fluoro-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-4-yl-piperazine-1-carboxamidine hydrochloride **516**

In accordance with the general Scheme 2A, the following is the preparation of a compound of Structure 5A, wherein each of  $R^{2a}$ ,  $R^{2b}$  and  $R^{2c}$  is hydrogen,  $m = 2$ ,  $n = 1$ ; Z is N; Y is *n*-pyridin-4-yl-carboxamidine; and  $R^1$  is 4-fluoro-1-naphthyl.

Triethylamine (758 mg, 7.5 mmol) was added to a solution **514** (811 mg, 1.5 mmol), as produced in Example 33, in anhydrous tetrahydrofuran (6 mL) and the resulting suspension cooled to 0° C. A solution of 4-ethoxymethylene-2-(4-fluoro-naphthalen-1-yl)-4H-oxazol-5-one (428 mg, 1.5 mmol) in tetrahydrofuran (6 mL) was added and the mixture stirred for 1h and evaporated under reduced pressure to yield a residue. The resulting residue was dissolved in tetrahydrofuran (5 mL) and 4 M hydrochloric acid in dioxane (2 mL) added. The resulting precipitate was collected by filtration, washed on the filter with 20% diethyl ether/methyl *tert*-butyl ether and dried under vacuum to yield the desired product **516** (349 mg).  $MH^+$  444;  $^1H$  NMR (DMSO  $d_6$ )  $\delta$  9.30 (m, 1H), 8.60 (m, 1H), 8.15 (m, 3H), 7.80 (m, 3H), 7.5 (m, 4H), 4.60 (m, 2H), 3.9 (m, 6H).

Similarly, substituting 4-ethoxymethylene-2-(4-fluoro-naphthalen-1-yl)-4H-oxazol-5-one with other oxazolones and following the procedure described in Example 34 the following compound was prepared:

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyridin-4-yl-piperazine-1-carboxamide hydrochloride **518**.  $MH^+$  427;  $^1HNMR$  (DMSO  $d_6$ )  $\delta$  9.20 (m, 2H), 8.60 (m, 2H), 8.15 (m, 3H), 7.60 (m, 5H), 4.60 (m, 2H), 3.9 (m, 6H).

### Example 35

#### N-Pyridin-3-yl-piperazine-1-carboxamide trifluoroacetate **520**

In accordance with the general Scheme 2A, the following is the preparation of a compound of Structure 4A, wherein each of  $R^{2a}$ ,  $R^{2b}$  and  $R^{2c}$  is hydrogen,  $m = 2$ ,  $n = 1$ ; Z is N; and Y is N-pyridin-3-yl-carboxamide.

A mixture of 1-(3-pyridyl)thiourea (3.45 g, 22.5 mmol), N-*tert*-butoxycarbonyl-piperazine (4.60 g, 24.7 mmol) and 1,3-dicyclohexylcarbodiimide (5.40 g, 26.2 mmol) in anhydrous tetrahydrofuran (150 mL) under a nitrogen atmosphere was refluxed for 48 h, cooled to room temperature and the solvent removed under reduced pressure to yield an oily residue. The only residue was triturated with water (2 x 50 mL) and filtered. The aqueous filtrate was concentrated to give a white solid (1.50 g). The resulting white solid was

- 97 -

suspended in toluene and sonicated, the precipitate was filtered and the filtrate concentrated under reduced pressure yielding a pale solid (920 mg).

The resulting pale solid (378 mmol) was treated with 50% trifluoroacetic acid/dichloromethane for 3 h. Removal of the solvent followed by trituration with methyl *tert*-butyl ether yielded the desired product as a crystalline solid that was collected by filtration and dried under vacuum **520**. (MH<sup>+</sup> 206).

### Example 36

#### 4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyridin-3-yl-piperazine-1-carboxamide hydrochloride **522**

In accordance with the general Scheme 2A, the following is the preparation of a compound of Structure 5A, wherein each of R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> is hydrogen, m = 2, n = 1; Z is N; Y is N-pyridin-3-yl-carboxamide; and R<sup>1</sup> is naphthyl.

To a solution of **520** (346 mg, 0.63 mmol), prepared as described in Example 35, in anhydrous tetrahydrofuran (5 mL), triethylamine (600 mL, 3.1 mmol) was added, followed by a solution of 4-ethoxymethylene-2-naphthalen-1-yl-4H-oxazol-5-one (169 mg, 0.63 mmol) in tetrahydrofuran (3 mL). The mixture was stirred for 30 min and the volatile materials were removed under reduced pressure to yield residue. The resulting residue was dissolved in tetrahydrofuran (5 mL) and 4 M hydrochloric acid in dioxane (2 mL) added. The resulting precipitate was collected by filtration, washed with 20% diethyl ether/methyl *tert*-butyl ether and dried under vacuum to yield the desired product as its hydrochloride salt **522** (43 mg). MH<sup>+</sup> 427; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 9.28 (d, 1H), 8.50 (m, 2H), 8.15 (m, 1H), 8.03 (m, 1H), 7.98 (m, 1H), 7.78 (m, 1H), 7.60 (m, 4H), 7.45 (s, 1H), 4.85 (m, 2H), 3.9 (m, 6H).



Example 374-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyrimidin-2-yl-piperazine-1-carboxamidinium hydrochloride 524

5 In accordance with the general Scheme 3A, the following is the preparation of a compound of Structure 5A, wherein each of R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> is hydrogen, m = 2, n = 1; Z is N; Y is N-pyrimidin-2-yl-carboxamidinium; and R<sup>1</sup> is naphthyl.

A mixture 1H-pyrrole-1-carboxamidinium hydrochloride (4.40 g, 30 mmol), N-  
10 *tert*-butoxycarbonyl piperazine (5.59 g, 30 mmol) and N,N-diisopropylethylamine (6.3 mL, 36 mmol) in 2-propanol (50 mL) was refluxed for 24 h, cooled to room temperature and the solvents were removed under reduced pressure. The residue was suspended in acetonitrile (50 mL) and filtered; the white precipitate was washed with acetonitrile (50 mL) and dried under vacuum to yield N-*tert*-  
15 *butoxycarbonyl piperazine-1-carboxamidinium* (6.20 g).

To a mixture of N-*tert*-butoxycarbonyl piperazine-1-carboxamidinium (228 mg, 1 mmol) and 2-chloropyrimidine (172 mg, 1.5 mmol) in anhydrous dioxane (2 mL), 60% NaH (80 mg, 2 mmol) was added. The reaction mixture was refluxed for 2 h, cooled to room temperature and concentrated to give a yellow oil. The oil  
20 was washed with methyl *tert*-butyl ether, followed by water, to yield a yellow precipitate of the desired intermediate (113 mg).

The yellow precipitate was treated with 50% trifluoroacetic acid/dichloromethane (1.5 mL) at room temperature for 1 h. The solvents were removed under reduced pressure, the residue washed with methyl *tert*-butyl  
25 ether and dried under vacuum yielding the desired piperazine intermediate as its trifluoroacetate salt (204 mg).

To a solution of the piperazine intermediate (180 mg, 0.33 mmol) in anhydrous tetrahydrofuran (5 mL), triethylamine (200 mL, 1.6 mmol) was added, followed by a solution of 4-ethoxymethylene-2-naphthalen-1-yl-4H-oxazol-5-one  
30 (89 mg, 0.33 mmol) in tetrahydrofuran (3 mL). The mixture was stirred for 20 min and the volatile materials were removed under reduced pressure. The residue was dissolved in tetrahydrofuran (5 mL) and 4 M hydrochloric acid in dioxane (2

mL) was added. The resulting precipitate was collected by filtration, washed with 50% ethanol/methyl *tert*-butyl ether and dried under vacuum to yield the desired product (100 mg) as its hydrochloride salt **524** (43 mg).  $M^+$  428;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  9.28 (d, 1H), 8.85 (d, 2H), 8.15 (d, 1H), 8.00 (m, 2H), 7.60 (m, 3H),  
5 7.45 (s, 1H), 7.30 (m, 1H), 4.85 (m, 2H), 3.9 (m, 6H).

Similarly, substituting 2-chloropyrimidine with 2-chloropyrazine, 4,6-dichloropyrimidine and the like, and 4-ethoxymethylene-2-naphthalen-1-yl-4H-oxazol-5-one with other oxazolones, following the procedure described in Example 37, the following examples were prepared:

10 4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyrazin-2-yl-piperazine-1-carboxamide hydrochloride **526**;  $M^+$  428;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  9.20 (d, 1H), 8.75 (s, 1H), 8.55 (m, 2H), 8.15 (d, 1H), 7.90 (m, 2H), 7.50 (m, 3H), 7.40 (s, 1H), 4.70 (m, 2H), 3.85 (m, 6H); and

15 N-(6-Chloro-pyrimidin-4-yl)-4-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxamide hydrochloride **528**;  $M^+$  461.97;  $^1\text{H}$  NMR ( $\text{DMSO } d_6$ )  $\delta$  9.30 (br. s, 1H), 9.20 (d, 1H), 8.80 (s, 1H), 8.1 (m, 3H), 7.70 (m, 4H), 7.40 (s, 1H), 4.60 (m, 2H), 3.95 (m, 6H).

### Example 38

20

#### 4-(4-Amino-piperidin-1-ylmethylene)-2-naphthalen-1-yl-4H-oxazol-5-one **530**

In accordance with the general Scheme 3A, the following is the preparation of a compound of Structure 5A, wherein each of  $R^{2a}$ ,  $R^{2b}$  and  $R^{2c}$  is hydrogen,  $m = 2$ ,  $n = 1$ ; Z is CH; Y is amino; and  $R^1$  is naphthyl.

25 To a solution of 4-ethoxymethylene-2-naphthalen-1-yl-4H-oxazol-5-one (6.30 g, 23.7 mmol) in tetrahydrofuran, piperidin-4-yl-carbamic acid *tert*-butyl ester (4.70 g, 23.7 mmol) was added, and the mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure to yield [1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-  
30 4-yl]-carbamic acid *tert*-butyl ester.

[1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-yl]-carbamic acid *tert*-butyl ester was stirred overnight in 20% trifluoroacetic

acid/dichloromethane at room temperature. Neutralization with triethylamine afforded a precipitate that was collected by filtration, washed with cold methyl *tert*-butyl ether and dried under vacuum yielding the desired product **530** (6.70 g), (MH<sup>+</sup> 322).

5

### Example 39

#### 4-(4-Aminomethyl-piperidin-1-ylmethylene)- 2-naphthalen-1-yl-4H-oxazol-5-one 532

10 In accordance with the general Scheme 3A, the following is the preparation of a compound of Structure 5A, wherein each of R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> is hydrogen, m = 2, n = 1; Z is CH; Y is aminomethyl; and R<sup>1</sup> is naphthyl.

To a solution of 4-ethoxymethylene-2-naphthalen-1-yl-4H-oxazol-5-one (11.40 g, 43 mmol) in tetrahydrofuran, benzylidene-piperidin-4-ylmethyl-amine  
15 (8.60 g, 43 mmol) was added, and the mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure to yield 4-{4-[(benzylidene-amino)-methyl]-piperidin-1-ylmethylene}-2-naphthalen-1-yl-4H-oxazol-5-one.

4-{4-[(benzylidene-amino)-methyl]-piperidin-1-ylmethylene}-2-naphthalen-  
20 1-yl-4H-oxazol-5-one was stirred overnight in 20% trifluoroacetic acid, 10% water in dichloromethane at room temperature. The resulting mixture was neutralized using aqueous sodium carbonate (250 mL), the resulting precipitate collected by filtration and washed with cold methyl *tert*-butyl ether. Recrystallization from dioxane yielded the desired product **532** (11.0 g); (MH<sup>+</sup> 336).

25

### Example 40

#### Furan-2-carboxylic acid [1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)- piperidin-4-yl]-amide 534

30 In accordance with the general Scheme 3A, the following is the preparation of a compound of Structure 5A, wherein each of R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> is hydrogen, m = 2, n = 1; Z is CH; Y is furan-2-yl-amide; and R<sup>1</sup> is naphthyl.

A 0.5 M acetonitrile solution of N,N-diisopropylethylamine (200  $\mu$ L) was added to a 1.25 M acetonitrile solution of **530** (200  $\mu$ L), prepared as described in Example 38. A 0.25 M tetrahydrofuran solution of 2-furanoyl chloride (300  $\mu$ L) was added, the reaction vessel sealed, and the mixture was maintained at 60° C for 24 h. The volatile materials were removed under high vacuum to yield the desired product **534** ( $MH^+$  416).

Similarly, substituting 4-(4-amino-piperidin-1-ylmethylene)-2-naphthalen-1-yl-4H-oxazol-5-one with 4-(4-aminomethyl-piperidin-1-ylmethylene)-2-naphthalen-1-yl-4H-oxazol-5-one, and 2-furanoyl chloride with other acid chlorides, following the procedure described in Example 40, the following examples were prepared:

N-[1-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-ylmethyl]-isobutyramide **536** ( $MH^+$  406);

N-[1-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-yl]-isobutyramide **538** ( $MH^+$  392);

Cyclohexanecarboxylic acid [1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-yl]-amide **540** ( $MH^+$  432);

3-Methyl-N-[1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-ylmethyl]-butyramide **542** ( $MH^+$  420);

3-Methyl-N-[1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-yl]-butyramide **544** ( $MH^+$  406);

Furan-2-carboxylic acid [1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-ylmethyl]-amide **546** ( $MH^+$  430); and

2-Methoxy-N-[1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-yl]-benzamide **548** ( $MH^+$  456).

Example 411-[1-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-ylmethyl]-  
3-(3,4,5-trimethoxy-phenyl)-urea 550

5 In accordance with the general Scheme 3A, the following is the preparation of a compound of Structure 5A, wherein each of R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> is hydrogen, m = 2, n = 1; Z is CH; Y is aminomethyl; and R<sup>1</sup> is naphthyl.

To a 1.25 M acetonitrile solution of 532 (200 µL), prepared as described in Example 39, a 0.5 M acetonitrile solution of N,N-diisopropylethylamine (200 µL)  
10 was added, followed by a 0.25 M tetrahydrofuran solution of 3,4,5-trimethoxy-phenyl isocyanate (300 µL). The reaction vessel was sealed and the mixture was maintained at 60° C for 24 h, cooled to room temperature and the volatile materials removed under high vacuum yielding the desired product 550 (MH<sup>+</sup> 545).

15 Similarly, substituting 4-(4-amino-piperidin-1-ylmethylene)-2-naphthalen-1-yl-4H-oxazol-5-one for 4-(4-aminomethyl-piperidin-1-ylmethylene)-2-naphthalen-1-yl-4H-oxazol-5-one, and 3,4,5-trimethoxy-phenyl isocyanate with other isocyanates, following the procedure described in Example 41, the following examples were prepared:

20 1-Benzoyl-3-[1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-yl]-urea 552 (MH<sup>+</sup> 470);

1-Cyclohexyl-3-[1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-yl]-urea 554 (MH<sup>+</sup> 448);

25 1-[1-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-yl]-3-phenethyl-urea 556 (MH<sup>+</sup> 470);

1-(2-Methoxy-phenyl)-3-[1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-ylmethyl]-urea 558 (MH<sup>+</sup> 484);

3-{3-[1-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-yl]-ureido}-propionic acid ethyl ester 560 (MH<sup>+</sup> 465);

30 1-(4-Methoxy-phenyl)-3-[1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-yl]-urea 562 (MH<sup>+</sup> 471); and

1-[1-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-yl]-3-phenyl-urea **564** ( $MH^+$  441).

Example 42

5

Naphthalene-2-sulfonic acid [1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-ylmethyl]-amide **566**

In accordance with the general Scheme 3A, the following is the preparation of a compound of Structure 5A, wherein each of  $R^{2a}$ ,  $R^{2b}$  and  $R^{2c}$  is hydrogen,  $m = 2$ ,  $n = 1$ ; Z is CH; Y is naphthylsulfonamide; and  $R^1$  is naphthyl.

To a 0.25 M acetonitrile solution of **532** (200  $\mu$ L), prepared as described in Example 39, a 0.5 M acetonitrile solution of N, N-diisopropylethylamine (200  $\mu$ L) was added, followed by a 0.25 M acetonitrile solution of naphthalene-2-sulfonyl chloride (300  $\mu$ L). The reaction vessel was sealed and the mixture was maintained at room temperature for 24 h. The volatile materials were removed under high vacuum yielding the desired product **566** ( $MH^+$  526).

Similarly, substituting 4-(4-amino-piperidin-1-ylmethylene)-2-naphthalen-1-yl-4H-oxazol-5-one for 4-(4-aminomethyl-piperidin-1-ylmethylene)-2-naphthalen-1-yl-4H-oxazol-5-one, and naphthalene-2-sulfonyl chloride with other sulfonyl chlorides, following the procedure described in Example 42, the following examples were prepared:

5-Dimethylamino-naphthalene-1-sulfonic acid [1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-ylmethyl]-amide **568** ( $MH^+$  570);

4-Fluoro-N-[1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-ylmethyl]-benzenesulfonamide **570** ( $MH^+$  495);

Benzo[1,2,5]thiadiazole-4-sulfonic acid [1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-ylmethyl]-amide **572** ( $MH^+$  434);

Naphthalene-2-sulfonic acid [1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-yl]-amide **574** ( $MH^+$  513);

Quinoline-8-sulfonic acid [1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-ylmethyl]-amide **576** ( $MH^+$  527);

4-Bromo-N-[1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-ylmethyl]-benzenesulfonamide **578** ( $MH^+$  555);

5-Dimethylamino-naphthalene-1-sulfonic acid [1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-yl]-amide **580** ( $MH^+$  555).

5

### Example 43

#### [1-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-yl]- carbamic acid cyclopentyl ester **582**

10 In accordance with the general Scheme 3A, the following is the preparation of a compound of Structure 5A, wherein each of  $R^{2a}$ ,  $R^{2b}$  and  $R^{2c}$  is hydrogen,  $m = 2$ ,  $n = 1$ ; Z is CH; Y is cyclopentyl carbamate; and  $R^1$  is naphthyl.

To a 0.25 M DMF solution of **530** (200  $\mu$ L), prepared as described in Example 38, a 0.5 M tetrahydrofuran solution of N,N-diisopropylethylamine (200  
15  $\mu$ L) was added, followed by a 0.25 M tetrahydrofuran solution of cyclopentyl chloroformate (300  $\mu$ L). The reaction vessel sealed and the mixture was maintained at room temperature for 24 h. The volatile materials were removed under high vacuum and the desired product utilized without further purification **582** ( $MH^+$  434).

20 Similarly, substituting 4-(4-amino-piperidin-1-ylmethylene)-2-naphthalen-1-yl-4H-oxazol-5-one with 4-(4-aminomethyl-piperidin-1-ylmethylene)-2-naphthalen-1-yl-4H-oxazol-5-one, and cyclopentyl chloroformate with other chloroformates, following the procedure described in Example 43, the following examples were prepared:

25 [1-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-ylmethyl]-carbamic acid methyl ester **584** ( $MH^+$  394);

[1-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-yl]-carbamic acid methyl ester **586** ( $MH^+$  380);

[1-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-yl]-  
30 carbamic acid isopropyl ester **588** ( $MH^+$  408);

[1-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-ylmethyl]-carbamic acid phenyl ester **590** ( $MH^+$  456);

[1-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-yl]-  
carbamic acid isobutyl ester **592** ( $\text{MH}^+$  422);

[1-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-yl]-  
carbamic acid phenyl ester **594** ( $\text{MH}^+$  442); and

5 [1-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidin-4-ylmethyl]-  
carbamic acid isopropyl ester **596** ( $\text{MH}^+$  422).

#### Example 44

10 1-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidine-  
4-carboxylic acid phenylamide **598**

In accordance with the general Scheme 2A, the following is the  
preparation of a compound of Structure 5A, wherein each of  $\text{R}^{2a}$ ,  $\text{R}^{2b}$  and  $\text{R}^{2c}$  is  
hydrogen,  $m = 2$ ,  $n = 1$ ; Z is CH; Y is N-phenylamide; and  $\text{R}^1$  is naphthyl.

15 A mixture of aniline (372 mg, 4 mmol), N-*tert*-butoxycarbonyl-isonipecotic  
acid (917 mg, 4 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.80  
g, 3 mmol) in dichloromethane (15 mL) was stirred at room temperature under an  
argon atmosphere overnight. The reaction mixture was diluted with  
dichloromethane and the organic solution was washed with cold 1M aqueous  
20 hydrochloric acid, water, saturated aqueous sodium bicarbonate, brine, dried  
over anhydrous sodium sulphate, filtered and evaporated under reduced  
pressure. The residue was recrystallized from ether yielding a white solid (1.06  
g).

The resulting white solid was treated with 50% trifluoroacetic acid/  
25 dichloromethane (15 mL) at room temperature overnight. The volatile materials  
were removed under high vacuum and the residue was azeotroped with toluene.  
To the resulting solid was added diethyl ether (15 mL) followed by triethylamine  
(1 mL), the mixture was set aside and the resulting precipitate collected by  
filtration.

30 To a solution of the resulting precipitate (406 mg, 2 mmol) in acetonitrile (8  
mL), triethylamine (0.5 mL) was added, followed by a solution of 4-  
ethoxymethylene-2-naphthalen-1-yl-4H-oxazol-5-one (534 mg, 2 mmol) in



acetonitrile (8 mL), and the resulting mixture was stirred at room temperature for 4 h. Concentration of the reaction mixture to approximately half its volume afforded a yellow precipitate that was collected by filtration and dried under vacuum yielding 1-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperidine-4-carboxylic acid phenylamide **598** (500 mg).  $MH^+$  426;  $^1H$  NMR: (DMSO  $d_6$ ):  $\delta$  1.98 (m, 2H), 2.19 (m, 2H), 2.90 (m, 1H), 3.65 (t, 2H), 4.18 (d, 1H), 5.58 (d, 2H), 7.20 (m, 1H), 7.45 (m, 2H), 7.60 (s, 1H), 7.70 (m, 6H), 8.15 (m, 4H), 9.30 (d, 1H), 10.00 (s, 1H).

10

### Example 45

#### $[^3H]$ prazosin Binding ( $\alpha_1$ -Adrenoceptor) Assay

$\alpha_{1A}$ -,  $\alpha_{1B}$ -, and  $\alpha_{1D}$ -adrenoceptor transfected CHO-K1 cells, prepared using the methods described in Chang et al. (1998) *FEBS Lett.* 422:279-283, were grown to confluence in T-162 tissue culture flasks in Ham's F-12 culture medium supplemented with 10% fetal bovine serum, geneticin (150  $\mu g/mL$ ) and streptomycin/penicillin (30  $\mu g/mL$ /30  $\mu g/mL$ ) at 37° C in 7%  $CO_2$ . Cells were harvested by incubating with phosphate-buffered saline (PBS) containing 30  $\mu M$  EDTA for 5 to 10 minutes at 37° C. Cells were pelleted by centrifuging at 500 x g for 5min, the pelleted cells were homogenized (Polytron homogenizer) in 10 vols (w/v) of 50 mM Tris, 1 mM EDTA, (homogenisation buffer, pH 7.4 at 4° C). The homogenate was centrifuged at 45,000 x g for 20 min. The pellet was resuspended in the homogenizing buffer and rehomogenized. The resulting homogenate was centrifuged at 45,000 x g for 20 min. The pellet was resuspended in 50 mM Tris buffer (pH 7.4 at 4° C), aliquoted, frozen, and stored at -80° C for further use.

The membranes were thawed at room temperature and diluted in assay buffer (50 mM Tris buffer at pH 4) at 37°C and homogenized using the Polytron tissue disrupter. The membranes were incubated with the radioligand ( $[^3H]$ prazosin, NEN, 0.1 - 0.5 nM) and test compound at 37°C for 30 min. The membranes were then filtered over polyethyleneimine-treated GF/B unifier plates using a Packard Filtermate Harvester and washed with ice-cold 50 mM

Tris-HCl, 1 mM EDTA buffer (3 x 3 sec. washes). Scintillation cocktail was added to the filter plates and bound radioligand determined by liquid scintillation spectrophotometry.

For each experiment, total binding (in the absence of any test or reference compounds) and non-specific binding (10  $\mu$ M phentolamine) were determined. For each sample tested, the concentration producing 50% inhibition of binding ( $IC_{50}$ ) and Hill Slope ( $n_H$ ) was determined using iterative non-linear curve fitting techniques with Kaleidagraph (Synergy Software) or other appropriate software. If the radioligand  $K_D$  was known, the inhibition dissociation constant ( $K_i$ ) of each ligand was determined according to the method of Cheng and Prusoff (Cheng, Y-C. and Prusoff, W.H., *Biochem. Pharmacol.*, (1973), 22:3099-3108).

Compounds of Formula (I) were tested using this assay and found to be selective  $\alpha_{1B}$ -adrenoceptor antagonists.

#### Example 46

##### Rat In Vivo, Blood Pressure Assay

The following describes an in vivo assay for measuring the effect of test compounds on blood pressure in normotensive and spontaneously hypertensive rats.

Normotensive or spontaneously hypertensive rats (0.25 to 0.45 kg) were fasted for 18 h and anesthetized with ether. The right femoral vein was isolated and cannulated with a fluid filled polyethylene cannulae for bolus administration of test substances. The right femoral artery was isolated and cannulated with a fluid filled polyethylene cannula connected to an external pressure transducer for monitoring mean arterial blood pressure (MAP).

Following cannulation, rats are pretreated (intravenous route) with an angiotensin receptor antagonist, a beta-adrenergic receptor antagonist and an  $\alpha_2$ -adrenergic receptor antagonist as described in Blue et al. (*Br. J. Pharmacol.* 120:107P).

The rats were placed in restrainers and allowed to recover from anesthesia. Following a 30-60 minute period for stabilization, the test compounds

- 108 -

or vehicles were administered intravenously. Following the last dose of test compound, prazosin was optionally administered, i.v., to determine hypotensive effects obtained by non-subtype-selective blockade of  $\alpha_1$ -adrenoceptors. Blood pressure and heart rate were monitored continuously for at least 4 h post-administration.

Compounds of Formula (I) were tested using this assay and found to be considerably less potent than prazosin at producing blood pressure lowering effects.

10

#### Example 47

##### Pain Response to Radiant Heat in Neuropathic Rats

The following describes an in vivo assay for measuring the effect of test compounds on the pain response to radiant heat in neuropathic rats.

Male Sprague-Dawley rats (Harlan, 240-300 g) were surgically prepared to have a chronic constriction injury (CCI) as described herein 13-15 days prior to testing. Rats were selected for the study according to the following criteria: ligated leg ( $L_L$ ) latency - 4 to 14 seconds; sham leg ( $L_S$ ) latency - 6 to 18 seconds; difference ( $L_{Diff} = L_L - L_S$ ) - greater than 1.5 seconds. Selected rats were randomly assigned to treatment groups and dosed at 0 (vehicle, 10 mL/kg, 0.5% CMC, 30, 60, 100 or 300  $\mu$ g/kg, *i.p.* After 1 hour post-dosing, rats were placed under inverted plastic cages on an elevated glass platform. For each rat, four trials of each of the following were performed: shone light on the left hind paw (sham) and recorded the latency when the paw was withdrawn; shone light on the right hind paw (ligated) and recorded the latency when the paw was withdrawn. Five minute intervals were allowed between trials. Hind paws were examined for redness and blistering after each test.

Compounds of Formula I were tested using this assay and found to have a significant effect in the radiant heat assay.

Thus, e.g. the results from these test experiments indicate that 4-(2-benzofuran-7-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamidine

hydrochloride (see Example 20) had a significant effect in the radiant heat assay at the 60, 100 and 300 µg/kg doses. It is therefore a selective  $\alpha_{1B}$ -adrenergic receptor antagonist.

A further experiment was conducted to evaluate the effects of 4-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamidine, and similar or related compounds, on the pain response to radiant heat in neuropathic rats.

4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamidine was prepared as described in Example 19. The compound has been identified as a selective  $\alpha_{1B}$ -adrenergic receptor antagonist using the methods described in Example 45.

Male Sprague-Dawley rats (Harlan, 240-300 g), were surgically prepared to have a CCI as described above 19-21 days prior to testing. Selected rats were randomly assigned to treatment groups and dosed with 4-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamidine at 0 (vehicle, 10 mL/kg deionized water, 30, 60, 100, 300 or 1000 µg/kg, *i.p.* After 1 hour post-dosing, rats were tested as described above.

The results from these experiments indicate that 4-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamidine had a significant effect in the radiant heat assay at the 60, 100, 300 and 1000 µg/kg doses.

#### Example 48

##### Cold Allodynia Response in Neuropathic Rats

The following describes an *in vivo* assay for measuring the effect of test compounds on the cold allodynia response in neuropathic rats.

Male Sprague-Dawley rats (Harlan, 160-200 g) were surgically prepared to have a chronic constriction injury (CCI) as described herein 6 days prior to testing. Rats were selected for the study according to the following criteria: 1) the average of two trials was less than or equal to 13 sec; and 2) there was consistency across the two trial scores. Animals were screened for

hypersensitivity to cold on post-surgery days 4 through 10, and selected for inclusion in dose-response studies based on the criteria described herein. The pre-dose screening values were used as the animals' baseline cold allodynia scores.

5        Selected rats were tested twice in the cold bath assay described herein for a pre-dose baseline and randomly assigned to treatment groups and dosed at 0 (vehicle, 10 mL/kg, 0.5% CMC, 30, 100 or 300 µg/kg, *i.p.* After 1 hour and 3 hours post-dosing, rats were tested in the cold bath assay. For each rat, the assay was run once at 1 and 3 hours post-dose. The time to raise the rear leg  
10        was recorded in each trial. The maximal observing time in each trial was 20 seconds.

Compounds of Formula (I) were tested using this assay and found to have a significant effect in the cold allodynia response assay.

In particular the results from these experiments indicate that, at 1 hour post-  
15        dose, 4-(2-benzofuran-7-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamide hydrochloride at the doses of 100 and 300 µg/kg both were significantly higher than vehicle as to the changes from pre-dose, viz. actual latency times (both  $p < 0.01$ ). At 3 hours post-dose the compound at 300 µg/kg was significantly higher than vehicle as to the changes from pre-dose ( $p < 0.05$ ).

20        Another experiment was conducted to evaluate the effects of 4-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamide on the cold allodynia response in neuropathic rats.

Male Sprague-Dawley rats (Harlan), 160-270 g, were surgically prepared to have a chronic constriction injury (CCI) as described above 5 days prior to testing.

25        Selected rats were dosed at 0 (vehicle, 10 mL/kg, deionized water), 30 or 300 µg/kg, *i.p.* After 20 min and 40 minutes post-dosing, rats were tested in the cold bath assay.

These results indicate that 4-(2-naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamide at 20 min post-dose exhibited a significant increase in latency from pre-dose when compared to the vehicle group at  
30        the both 30 and 300 µg/kg. At 40 min post-dose only the group receiving 300 µg/kg had a significant change from pre-dose when compared to vehicle at the same time point.

A further experiment was conducted to evaluate the effects of 3-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]-piperazin-1-yl}propyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione on the cold allodynia response in neuropathic rats. 3-(3-{4-[2-(2,2,2-Trifluoroethoxy)phenyl]-piperazin-1-yl}propyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione  
5 was prepared as described in Example 32 of U.S. Patent No. 5,859,014 to Bantle et al.

Male Sprague-Dawley rats (Harlan), 170-270 g, were surgically prepared to have a chronic constriction injury (CCI) as described above 14 days prior to testing. Selected rats were dosed at 0 (vehicle, 10 mL/kg, deionized water), 30 or 300 µg/kg,  
10 *i.p.* After 20 min and 40 minutes post-dosing, rats were tested in the cold bath assay.

The results from this experiment indicate that when compared with changes from pre-dose, only the group receiving 3-(3-{4-[2-(2,2,2-trifluoroethoxy)phenyl]-piperazin-1-yl}propyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione at 300 µg/kg showed a significant increase in latency times compared to the vehicle control at 40 min post-  
15 dose.

#### Example 49

The following are representative pharmaceutical formulations containing a  
20 compound identified as a selective  $\alpha_{1B}$ -adrenergic receptor antagonist such as a compound of Formula (I).

- 112 -

Tablet formulation

The following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet (mg)
compound of this invention	400
cornstarch	50
croscarmellose sodium	25
lactose	120
magnesium stearate	5

5

Capsule formulation

The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

Ingredient	Quantity per tablet (mg)
compound of this invention	200
lactose, spray-dried	148
magnesium stearate	2

10

- 113 -

Suspension formulation

The following ingredients are mixed to form a suspension for oral administration.

Ingredient	Amount
compound of this invention	1.0 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.15 g
propyl paraben	0.05 g
granulated sugar	25.5 g
sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
colorings	0.5 mg
distilled water	q.s. to 100 mL

5

Injectable formulation

The following ingredients are mixed to form an injectable formulation.

Ingredient	Amount
compound of this invention	0.2 g
sodium acetate buffer solution, 0.4 M	2. mL
HCl (1N) or NaOH (1N)	q.s. to suitable pH
water (distilled, sterile)	q.s. to 20 mL

10



- 114 -

Topical formulation

A topical formulation is prepared with the following ingredients:

Ingredient	Amount (g)
compound of this invention	10
Span 60	2
TWEEN®60	2
mineral oil	5
petrolatum	5
methyl paraben	0.15
propyl paraben	0.05
BHA (butylated hydroxy anisole)	0.01
distilled water	q.s. to 100 mL

- 5 All of the above ingredients, except water, are combined and heated to 60-70°C with stirring. A sufficient quantity of water at 60 °C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. to 100 g.

Suppository formulation

- 10 A suppository of total weight 2.5 g is prepared by mixing the compound of the invention with Witepsol® H-15 (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York), and has the following composition:

Ingredient	Amount
compound of this invention	500 mg
Witepsol® H-15	balance

- 15 Nasal Spray formulation

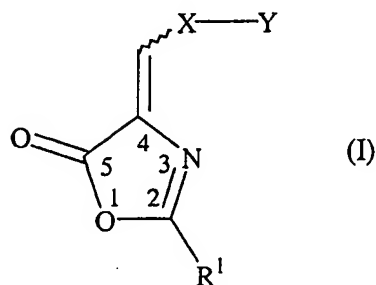
Several aqueous suspensions containing from 0.025-0.5 percent active compound are prepared as nasal spray formulations. The formulations optionally contain inactive ingredients such as microcrystalline cellulose, sodium

- 115 -

carboxymethylcellulose, dextrose, and the like. Hydrochloric acid may be added to adjust pH. The nasal spray formulations may be delivered via a nasal spray metered pump typically delivering 50-100 microliters of formulation per actuation. A typical dosing schedule is 2-4 sprays every 4-10 h.

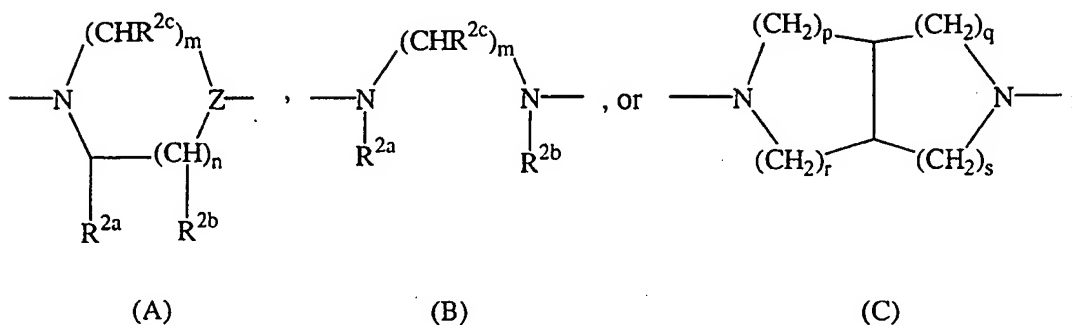
Claims

1. A compound comprising the Formula (I):



wherein:

X is Formula (A), (B) or (C):



m is an integer ranging from 1 to 6 inclusive;

n is an integer ranging from 0 to 5 inclusive;

p, q, r and s are each independently integers ranging from 1 to 3 inclusive, with the proviso that when p is greater than one, r is 1 and when s is greater than one, q is 1;

Y is  $-(CH_2)_w-R^3$ ,  $-(CH_2)_w-CO-R^4$ ,  $-(CH_2)_w-CO-NH-R^5$ ,  $-(CH_2)_w-C(NR^6)-NH-R^7$ ,

$-(CH_2)_w-SO_2-R^8$ ,  $-(CH_2)_w-NH-R^9$ ,  $-(CH_2)_w-NH-CO-R^{10}$ ,  $-(CH_2)_w-NH-CO-NH-R^{11}$ , or  $-(CH_2)_w-NH-SO_2-R^{12}$ ; wherein w is an integer ranging from 0 to 3 inclusive;

- 117 -

Z is CH or N;

R<sup>1</sup> is cycloalkyl, cycloalkenyl, heterocyclic, aryl or heteroaryl;

R<sup>2a</sup>, R<sup>2b</sup> or R<sup>2c</sup> are each independently in each occurrence hydrogen, alkyl, alkenyl, cycloalkyl, aryl, or arylalkyl; or R<sup>2a</sup> and R<sup>2b</sup> taken together with the  
 5 carbons to which they are attached form a 5- to 7-membered ring structure;

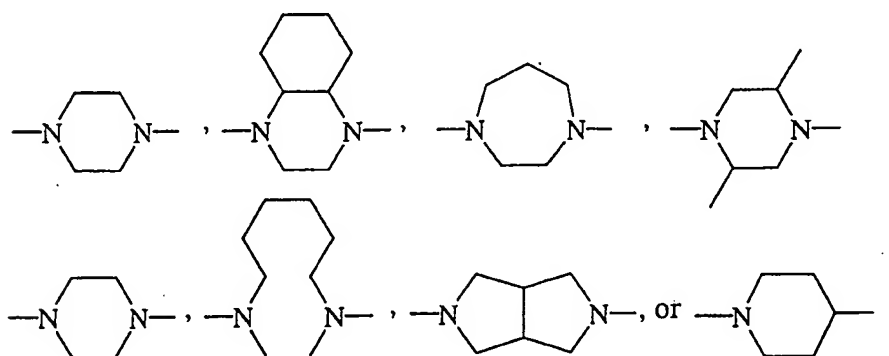
R<sup>3</sup> is heterocyclic or heteroaryl;

R<sup>4</sup>, R<sup>5</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup> are each independently in each occurrence hydrogen, alkyl, alkoxy, hydroxyalkyl, alkylthio, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocyclic, heterocyclicalkyl,  
 10 aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R<sup>6</sup> and R<sup>7</sup> are each independently in each occurrence hydrogen, alkyl, hydroxyalkyl, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocyclic, heterocyclicalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

or an individual isomer or a racemic or non-racemic mixture of isomers, or  
 15 a pharmaceutically acceptable salt or solvate thereof.

2. The compound of Claim 1, wherein X is:



20 or an individual isomer or a racemic or non-racemic mixture of isomers, or a pharmaceutically acceptable salt or solvate thereof.

3. The compound of Claim 2, wherein X is piperazinyl or piperidinyl; or an individual isomer or a racemic or non-racemic mixture of isomers, or a pharmaceutically acceptable salt or solvate thereof.

5 4. The compound of Claim 2 or Claim 3, wherein R<sup>1</sup> is aryl or heteroaryl; or an individual isomer or a racemic or non-racemic mixture of isomers, or a pharmaceutically acceptable salt or solvate thereof.

5. The compound of Claim 2 or Claim 3, wherein R<sup>1</sup> is an alkyl-, halo-  
10 or alkoxy-substituted phenyl, a bicyclic aryl or a bicyclic heteroaryl; or an individual isomer or a racemic or non-racemic mixture of isomers, or a pharmaceutically acceptable salt or solvate thereof.

6. The compound of Claim 2 or Claim 3, wherein R<sup>1</sup> is 3-  
15 methylphenyl, 3-chlorophenyl, 3-methoxyphenyl, naphthyl, fluoronaphthyl, thianaphthenyl, benzofuranyl, quinoliny, indolyl, fluorobenzofuranyl, or benzimidazolyl; or an individual isomer or a racemic or non-racemic mixture of isomers, or a pharmaceutically acceptable salt or solvate thereof.

20 7. The compound of Claim 4 or Claim 5, wherein Y is  $-(CH_2)_w-COR^4$ ,  $-(CH_2)_w-SO_2R^8$ ,  $-(CH_2)_w-NHR^9$ ,  $-(CH_2)_w-NHCOR^{10}$ ,  $-(CH_2)_w-NHCONHR^{11}$  or  $-(CH_2)_w-NHSO_2R^{12}$ ; or an individual isomer or a racemic or non-racemic mixture of isomers, or a pharmaceutically acceptable salt or solvate thereof.

25 8. The compound of Claim 7, wherein R<sup>1</sup> is 3-methylphenyl, 3-chlorophenyl, 3-methoxyphenyl, naphthyl, fluoronaphthyl, thianaphthenyl, benzofuranyl, quinoliny, indolyl, fluorobenzofuranyl or benzimidazolyl; R<sup>4</sup> is alkyl, alkoxy, cycloalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl; R<sup>8</sup> and R<sup>12</sup> are alkyl, aryl, arylalkyl, or heteroaryl; R<sup>9</sup> is alkyl, arylalkyl, or heteroarylalkyl; R<sup>10</sup> is  
30 alkyl, alkoxy, cycloalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl; R<sup>11</sup> is alkyl, cycloalkyl, heterocyclicalkyl, aryl, arylalkyl, or heteroaryl; or an individual isomer

or a racemic or non-racemic mixture of isomers, or a pharmaceutically acceptable salt or solvate thereof.

9. The compound of any one of Claim 2 to 6, wherein Y is  $-(CH_2)_w-R^3$  or  $-(CH_2)_w-CO-NH-R^5$  or  $-(CH_2)_w-C(NR^6)-NH-R^7$ ; or an individual isomer or a racemic or non-racemic mixture of isomers, or a pharmaceutically acceptable salt or solvate thereof.

10. The compound of Claim 9, wherein  $R^3$  is a moiety selected from benzooxazolyl, pyrazolyl, pyrimidyl, pyrrolyl, quinolinyl, isoquinolinyl, benzoisoquinolinyl dione, indolyl, imidazolyl, benzimidazolyl, imidazopyridinyl, oxazolyl, isooxazolyl, quinoxanilyl, thiazolyl, benzothiazolyl, or thiazolidinyl; wherein said moiety is optionally substituted with one or more of the following substituents: hydroxy, cyano, alkyl, alkoxy, thioalkyl, halo, haloalkyl, trifluoromethyl, hydroxyalkyl, alkoxycarbonyl, nitro, amino, alkylamino, dialkylamino, cycloalkyl, cycloalkylenyl, heterocyclic, aryl or heteroaryl; or an individual isomer or a racemic or non-racemic mixture of isomers, or a pharmaceutically acceptable salt or solvate thereof.

11. The compound of Claim 2 or 3, wherein Y is  $-(CH_2)_w-CO-NH-R^5$  and  $R^5$  is alkyl, cycloalkyl, heterocyclylalkyl, aryl, arylalkyl, or heteroaryl; or an individual isomer or a racemic or non-racemic mixture of isomers, or a pharmaceutically acceptable salt or solvate thereof.

12. The compound of Claim 2, wherein Y is  $-(CH_2)_w-C(NR^6)-NH-R^7$  and wherein  $R^6$  is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, or heteroaryl; or an individual isomer or a racemic or non-racemic mixture of isomers, or a pharmaceutically acceptable salt or solvate thereof.

13. The compound of claim 12, wherein  $R^7$  is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, or heteroaryl; or an individual isomer or a racemic or

non-racemic mixture of isomers, or a pharmaceutically acceptable salt or solvate thereof.

14. The compound of Claim 1, wherein the compound is:

- 5 4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid phenylamide;
- 4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-piperazine-1-carboxamidine;
- 4-(2-Naphthalen-1-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-10 1-carboxamidine;
- 4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-naphthalen-1-yl-4H-oxazol-5-one;
- 4-[2-(4-Fluoro-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide;
- 15 4-[2-(4-Fluoro-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamidine;
- 4-[2-(4-Fluoro-naphthalen-1-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-piperazine-1-carboxamidine;
- 4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(4-fluoro-20 naphthalen-1-yl)-4H-oxazol-5-one;
- 4-[4-(4,5-Dihydro-1H-imidazol-2-yl)-piperazin-1-ylmethylene]-2-(4-fluoro-naphthalen-1-yl)-4H-oxazol-5-one;
- 4-[2-(7-Fluoro-benzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide;
- 25 4-[2-(7-Fluoro-benzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamidine;
- 4-[2-(7-Fluoro-benzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-piperazine-1-carboxamidine;
- 4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(7-fluoro-30 benzofuran-4-yl)-4H-oxazol-5-one;
- 4-(2-Benzofuran-4-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid phenylamide;

4-(2-Benzofuran-4-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-piperazine-1-carboxamidine;

4-(2-Benzofuran-4-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamidine;

5        2-Benzofuran-4-yl-4-[4-(1H-benzoimidazol-2-yl)-piperazin-1-ylmethylene]-4H-oxazol-5-one;

4-[2-(2,3-Dihydro-benzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide;

10       4-[2-(2,3-Dihydro-benzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamidine;

4-[2-(2,3-Dihydro-benzofuran-4-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-phenyl-piperazine-1-carboxamidine;

4-(2-Benzofuran-7-yl-5-oxo-oxazol-4-ylidenemethyl)-piperazine-1-carboxylic acid phenylamide;

15       4-(2-Benzofuran-7-yl-5-oxo-oxazol-4-ylidenemethyl)-N-pyridin-2-yl-piperazine-1-carboxamidine;

4-(2-Benzofuran-7-yl-5-oxo-oxazol-4-ylidenemethyl)-N-phenyl-piperazine-1-carboxamidine;

20       2-Benzofuran-7-yl-4-[4-(4,5-dihydro-1H-imidazol-2-yl)-piperazin-1-ylmethylene]-4H-oxazol-5-one;

4-[2-(2,3-Dihydro-benzofuran-7-yl)-5-oxo-oxazol-4-ylidenemethyl]-piperazine-1-carboxylic acid phenylamide;

4-[2-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-5-oxo-oxazol-4-ylidenemethyl]-N-pyridin-2-yl-piperazine-1-carboxamidine;

25       4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-4H-oxazol-5-one;

2-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-4-[4-(4,5-dihydro-1H-imidazol-2-yl)-piperazin-1-ylmethylene]-4H-oxazol-5-one; or

30       4-[4-(1H-Benzoimidazol-2-yl)-piperazin-1-ylmethylene]-2-(4-fluoro-naphthalen-1-yl)-4H-oxazol-5-one;



an individual isomer, a racemic or non-racemic mixture of isomers, or a pharmaceutically acceptable salt or solvate thereof.

15        15.    A pharmaceutical composition comprising a therapeutically effective amount of the compound of any of Claims 1 to 14, in admixture with one or more pharmaceutically acceptable non-toxic carriers.

16.    The pharmaceutical composition of Claim 15, wherein the compound is an  $\alpha_1$ -adrenoceptor modulator.

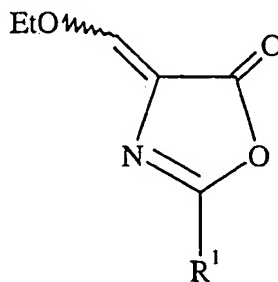
10

17.    The pharmaceutical composition of Claim 16, wherein the  $\alpha_1$ -adrenoceptor modulator is an  $\alpha_1$ -adrenoceptor antagonist or an  $\alpha_{1B}$ -adrenoceptor antagonist.

15

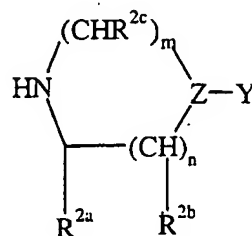
18.    The pharmaceutical composition of any one of Claims 15 to 17 for the treatment of disorders of the urinary tract such as an obstruction of the urinary tract, sexual dysfunction, pain, hypertension, or cardiac dysfunction.

19.    A process for preparing a compound as claimed in Claim 1 which process comprises reacting an  $R^1$ -substituted 4-ethoxy-methylene-5-oxazolone having the general formula



- 123 -

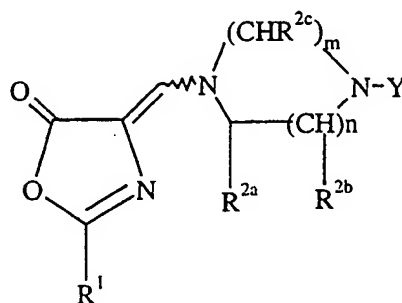
(i) with a compound of the general formula



4A

to provide a compound of the general formula

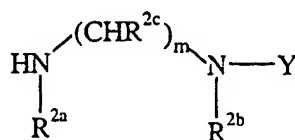
5



5A

or,

(ii) with a compound of the general formula

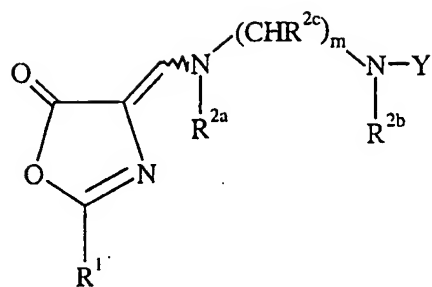


4B

10

to provide a compound of the general formula

- 124 -

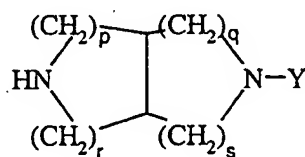


5B

or,

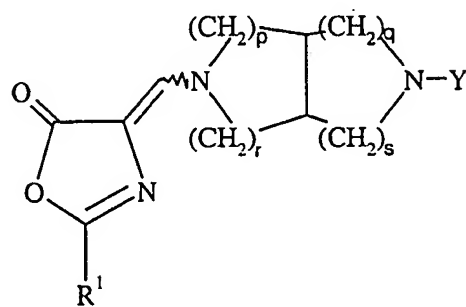
(iii) with a compound of the general formula

5



4C

to provide a compound of the general formula



5C

10 wherein the substituents and the indices are as defined in Claim 1.

20. A compound according to any one of Claims 1 to 14, whenever prepared by a process as claimed in Claim 19 or by an equivalent method.

21. The use of a compound as claimed in any one of Claims 1 to 14 for  
5 the treatment of diseases, such as disorders of the urinary tract, including obstruction of the urinary tract, sexual dysfunction, pain, hypertension, or cardiae dysfunction.

22. The use of compound as claimed in any one of Claims 1 to 14 for  
10 the preparation of a pharmaceutical composition containing a compound of formula (I) as specified in Claim 1 for the treatment of disorders of the urinary tract, such as obstruction of the urinary tract, sexual dysfunction, pain, hypertension, or cardiae dysfunction

15 23. The invention as hereinbefore described.

\*\*\*

# INTERNATIONAL SEARCH REPORT

Int. Appl. No.

PCT/EP 00/02200

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D263/42 C07D413/00 C07D417/00 C07D487/04 A61K31/421  
A61K31/422 A61P13/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 859 014 A (BANTLE G W ET AL) 12 January 1999 (1999-01-12) cited in the application the whole document	1,15-18
A	WO 96 16049 A (GLAXO WELLCOME INC.) 30 May 1996 (1996-05-30) cited in the application the whole document	1,15-18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

12 July 2000

Date of mailing of the international search report

27/07/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Allard, M

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 23 (partly)

Claim 23 does not clearly define the matter for which protection is sought, contrary to Article 6 PCT. The search with regard to this claim has therefore been limited to the subject-matter of claims 1-22.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/02200

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5859014	A	12-01-1999	NONE	
WO 9616049	A	30-05-1996	AU 4174096 A	17-06-1996
			EP 0793658 A	10-09-1997
			JP 10509713 T	22-09-1998
			ZA 9509855 A	07-08-1996